

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE, S.A. and  
ROCHE PALO ALTO, LLC,

Plaintiffs,

-vs-

DR. REDDY'S LABORATORIES, LTD.,  
DR. REDDY'S LABORATORIES, INC.,  
TEVA PHARMACEUTICALS USA, INC.,  
and TEVA PHARMACEUTICAL  
INDUSTRIES, LTD.

Defendants.

CIVIL ACTION NUMBER:

11-3962

TRIAL

Clarkson S. Fisher United States Courthouse  
402 East State Street  
Trenton, New Jersey 08608  
June 4, 2015

**B E F O R E:**

THE HONORABLE MARY L. COOPER  
UNITED STATES DISTRICT JUDGE

Certified as True and Correct as required by Title 28, U.S.C.,  
Section 753

/S/ Regina A. Berenato-Tell, CCR, CRR, RMR, RPR

/S/ Carol Farrell, CCR, CRR, RMR, CCP, RPR, RSA

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## I N D E X

<u>WITNESS</u>	<u>VOIR</u> <u>DIRE</u>	<u>DIRECT</u>	<u>CROSS</u>	<u>REDIRECT</u>	<u>RECROSS</u>
JOHN P. FRUEHAUF					
By Mr. Wong	4	14		183	
By Mr. O'Malley			107		204

—Voir Dire - Fruehauf—

1 (In open court. June 4, 2015, 9:30 a.m.)

2 THE COURT: Good morning, everyone. Okay. Are we  
3 ready to go to work today? Would you like to call your next  
4 witness?

5 MR. WONG: Yes. Good morning, Your Honor. My name  
6 is Jovial Wong. I represent the Teva defendants. Good to see  
7 you again.

8 As our first witness defendants call Dr. John Freuhauf.  
9 He will be discussing more about the efficacy of palonosetron.

10 (Whereupon, JOHN FRUEHAUF, witness for the  
11 defendants, sworn.)

12 THE DEPUTY CLERK: Please state and spell your full  
13 name for the record.

14 THE WITNESS: John P. Fruehauf, F-R-U-E-H-A-U-F.

15 VOIR DIRE EXAMINATION BY MR. WONG:

16 Q. Good morning, Dr. Fruehauf.

17 A. Good morning.

18 Q. Dr. Fruehauf, have you been asked to provide expert  
19 opinions in this case?

20 A. Yes, I have.

21 Q. And, in general, what do your opinions relate to?

22 A. They relate to the clinical development of palonosetron.

23 Q. Okay. Let's do a little background first, Dr. Fruehauf.

24 Where are you currently employed?

25 A. University of California Irvine.

—Voir Dire - Fruehauf—

1 Q. And what is your current position at the University of  
2 California Irvine?

3 A. I'm a professor of clinical medicine and the director of  
4 clinical pharmacology and developmental therapeutics.

5 Q. And is there a particular cancer center that you work at  
6 at UC, Irvine?

7 A. I work at the Chao Family Comprehensive Cancer Center.

8 Q. And what is a comprehensive cancer center?

9 A. It is a cancer center -- there are 43 comprehensive  
10 cancer centers in the United States, and this is one of those.  
11 They're designated by the National Cancer Institute, and they  
12 have to have the complete array of services from basic  
13 research to clinical trials development to qualify.

14 Q. How long have you been at UC, Irvine?

15 A. Since 1993.

16 Q. Can you briefly describe your educational history?

17 A. I went to college at UC Santa Barbara where I got a  
18 bachelor's degree in psychology and a bachelor's degree in  
19 cellular and organismal biology. And then I proceeded to  
20 medical school and did an M.D./Ph.D. program at Rush  
21 University in Chicago, and my Ph.D. was in pharmacology.

22 Q. What is pharmacology?

23 A. Pharmacology is the study of how drugs work.

24 Q. Okay. After you got your medical degree in 1985 what did  
25 you do?

—Voir Dire - Fruehauf—

1 THE COURT: Just a second. The Ph.D. was in what?

2 THE WITNESS: Pharmacology.

3 THE COURT: Okay. And the M.D. was an M.D.?

4 THE WITNESS: Yes, ma'am.

5 THE COURT: Then you went on to specialize in your  
6 medical training?

7 THE WITNESS: Yes. Then I did my residency at UC,  
8 Irvine, and then I went to do my fellowship. After two years  
9 of residency I was in the scientists' training track, so I did  
10 four years of medical oncology at the National Cancer  
11 Institute in Bethesda and then one more year in biotechnology  
12 there.

13 BY MR. WONG:

14 Q. Okay. While at the National Cancer Institute, did you  
15 participate in clinical trials?

16 A. Yes, I did. In fact, every patient who we saw at the  
17 cancer center had to be on a clinical trial.

18 Q. After your time at the National Cancer Institute what did  
19 you do?

20 A. Then I went to OncoTech, a biotechnology company.

21 Q. What was the focus of your work at OncoTech?

22 A. OncoTech was a company that -- the tumor from the patient  
23 would be sent to the laboratory, and we would study the  
24 effects of different chemotherapy agents that might be  
25 selected for that patient's tumor type. And we looked at the

—Voir Dire - Fruehauf—

1 impact of the drugs on the tumors growing in a test tube, so  
2 to speak, and then based on the results we could advise the  
3 clinician about, you know, which drug would be less likely or  
4 more likely to be effective for that patient.

5 Q. Okay. Did your work at OncoTech include drug product  
6 development?

7 A. Yes, it did. So, if there were residual tumor cells  
8 after performing the primary testing, then we worked with  
9 pharmaceutical companies to study their developmental  
10 compounds in a preclinical setting against the human tumors,  
11 which we felt was more representative than the typical cell  
12 lines that most companies would utilize.

13 Q. Okay. How long were you at OncoTech?

14 A. Until 2006.

15 Q. And where did you go after OncoTech?

16 A. I was working at both UC, Irvine -- as a medical  
17 oncologist -- and OncoTech, but I was part-time at the  
18 university until 2006, and then I went full-time at that year.

19 Q. Okay. Now, while at UC, Irvine, what has been the focus  
20 of your research?

21 A. Basically clinical trials, you know, to translate ideas  
22 from the laboratory into the clinic, writing clinical trials,  
23 carrying them out.

24 Q. Okay. What does the term or principle "bench-to-bedside"  
25 mean?

—Voir Dire - Fruehauf—

1 A. So, bench-to-bedside is really how we were trained at the  
2 NCI.

3 So you would go into the laboratory, do experiments  
4 with cell lines and drugs and then come up with maybe a new  
5 combination of treatments that you could then go and write a  
6 clinical trial and give it to the patients to see if it works  
7 better than what was there before.

8 Q. Okay. And what types of clinical trials do you carry out  
9 now?

10 A. I carry out various clinical trials in different  
11 diseases: Melanoma, urological oncology, kidney cancer,  
12 bladder cancer.

13 Q. Do you have experience carrying out all phases of  
14 clinical trials?

15 A. Yes. As director of developmental therapeutics, I'm  
16 involved in Phase I, Phase II, and Phase III trials.

17 THE COURT: What is Phase I, Doctor?

18 THE WITNESS: Phase I?

19 THE COURT: To you. You know, I hear what it is from  
20 lawyers and that kind of thing, but what does Phase I consist  
21 of in your experience?

22 THE WITNESS: Well, in my experience it is the first  
23 time you -- usually there's the first-in-man Phase I.

24 First-in-man. So, the first time you actually take a drug and  
25 give it to a human being before it has been given to animals



—Voir Dire - Fruehauf—

1 and put on cells, and this is the first time you're giving it  
2 to a person, so it is a safety question.

3 THE COURT: So, this is healthy volunteers?

4 THE WITNESS: In the perspective of the situation at  
5 hand that would be healthy volunteers.

6 THE COURT: Okay. Fine. Thank you.

7 BY MR. WONG:

8 Q. How many clinical trials are you currently involved with?

9 A. Seven or eight trials right now.

10 Q. And does your work at UC, Irvine also include preclinical  
11 trial work?

12 A. Yes. So, I mean, we -- you know, based on my prior  
13 laboratory experience at OncoTech I have continued to do the  
14 work of sort of correlating what happens in the test tube with  
15 what happens in people and trying to figure out are there  
16 markers we can study on the patient's tumor, like is there a  
17 mutation that would predict the drug will or won't work for  
18 that patient.

19 THE COURT: Do you have test tube laboratories in  
20 your --

21 THE WITNESS: Yes. I train Ph.D. students, so I have  
22 a regular, you know, bench laboratory where we grow the cells  
23 and tissue culture, and we add the drugs, and flow cytometry  
24 and HPLC and stuff like that.

25 BY MR. WONG:

—Voir Dire - Fruehauf—

1 Q. Getting back to your clinical practice in humans, how  
2 busy is your clinical practice?

3 A. I have three days a week that I see patients, and then  
4 there's a month every year that I'm in the inpatient service  
5 taking care of all the cancer patients in the hospital.

6 THE COURT: How do you do both, this kind of heavy  
7 research that you're doing, clinical trials and preclinical  
8 lab work, and also follow patient charts?

9 THE WITNESS: So, it is all about protected time.  
10 You know, you have to have some protected time to be able to  
11 go to the lab and talk to your post doc or graduate students  
12 about their experiments and review their data. You go to the  
13 clinic and, so, I have a really good nurse, and I have a good  
14 post doc, and those people help me tremendously in managing  
15 things on a daily level. So I become more of a supervisor.  
16 But the patient care takes the most time.

17 BY MR. WONG:

18 Q. Over in your entire career, about how many cancer  
19 patients do you think you have treated?

20 A. Oh, you know, more than 1,000.

21 Q. Now, as part of your clinical oncology practice do you  
22 have experience with supportive care of your patients?

23 A. Yes. At the time I trained at the National Cancer  
24 Institute there wasn't really a palliative care specialty yet,  
25 which does do supportive care today, and, so, we were trained

—Voir Dire - Fruehauf—

1 to support the patient with pain medications, antinausea  
2 medications, antidiarrheal medications just to really support  
3 the whole patient.

4 So, I grew up out of that experience, and, so, to this  
5 day I'm trying to manage the quality of life for the patient  
6 concomitantly with the intervention for their -- to treat  
7 their cancer.

8 Q. Okay. Can you explain your experience with antiemetics?

9 A. Unfortunately today we still use chemotherapy for the  
10 vast majority of cancer patients. And, so, as a result we  
11 need to be giving medications that will suppress nausea and  
12 vomiting.

13 And as research into the mechanisms of what causes this  
14 process in people, drugs have been developed that attack the  
15 different sort of pathways that stimulate nausea and vomiting.

16 So, today we sort of use an amalgam of agents that will  
17 attack different pathways so you're simultaneously suppressing  
18 the impulse to throw up and to feel sick.

19 So, there would be Marinol, for instance, for  
20 cannabinoid receptors; NK-1 -- Emend is an NK-1 receptor  
21 inhibitor; the 5-HT receptor inhibitors, such as palonosetron  
22 and Compazine. I give Compazine frequently, which is a  
23 dopamine receptor suppressor.

24 So, it is really combining drugs that work on different  
25 pieces of the process of nausea.

—Voir Dire - Fruehauf—

1 Q. Okay.

2 THE COURT: And these receptors are not just in the  
3 brain, right?

4 THE WITNESS: No. There's the gut process, which is  
5 where serotonin signaling starts in the body. It is all built  
6 on the concept of an evolution you don't want to eat poison.  
7 So when your gut senses a poison, your body wants to extrude  
8 it, so it sends a signal to the brain stem to throw up,  
9 basically.

10 BY MR. WONG:

11 Q. And in addition to your research at UC, Irvine do you  
12 also teach?

13 A. Yes. I teach an undergraduate class every fall, so it is  
14 coming up, and it is about 250 undergraduate students that are  
15 upper division. And I'm teaching --

16 THE COURT: These are not medical students?

17 THE WITNESS: No. This is undergraduates, and they  
18 are pharmaceutical sciences majors, and they're mostly  
19 prepharmacy, but there are subsets that are premed and  
20 preindustry. And I teach the fundamentals of drug  
21 development, the clinical phases of drug development, concepts  
22 of how does the membrane and the receptor work for drugs.  
23 Basic concepts that would help them in the future.

24 BY MR. WONG:

25 Q. Aside from undergrads, do you teach any other students?

—Voir Dire - Fruehauf—

1 A. Yes. So, I teach, of course, medical students,  
2 residents, and fellows. And next month I'll be giving a core  
3 lecture to the new fellows that are just starting on melanoma  
4 and how we approach melanoma. So, you know, I enjoy teaching.

5 Q. Okay. Do you teach your students about clinical trials?

6 A. Yes. So, the undergrad class, that's a big component of  
7 it, because so much of what you do as a pharmacist is you're,  
8 you know, giving drugs, and you need to know, sort of, how do  
9 we come up with these package inserts and how -- what does the  
10 drug have to go through to finally be accepted?

11 Q. Okay. Outside of UC, Irvine are you involved with any  
12 professional organizations in your field?

13 A. Yes. I'm a member of the American Society of Clinical  
14 Oncology, the American Association of Cancer Research, which  
15 are the two big meetings for sort of the bench and bedside  
16 presentations on results, and, you know, some local  
17 organizations.

18 Q. Okay. Have you also published papers in the field of  
19 oncology?

20 A. I have about 80 peer-reviewed publications.

21 Q. Okay. Are you yourself also a peer-reviewer on relevant  
22 journals?

23 A. Yes. I peer review articles. I got a text message this  
24 morning about I'm late on reviewing a manuscript, so I review  
25 for Cancer Research, Clinical Cancer Research, you know,

—Direct - Fruehauf—

1 various cancer journals.

2 Q. Okay. Have you ever served as an expert witness in a  
3 patent trial?

4 A. Yes, I have.

5 Q. How many?

6 A. In one trial.

7 Q. And in that trial, generally speaking, what was the  
8 expertise that you were offering?

9 A. It was about the preclinical and clinical development of  
10 pemetrexed.

11 MR. WONG: Your Honor, defendants tender Dr. Fruehauf  
12 as an expert in the clinical sciences and pharmacology with a  
13 focus on oncology and supportive care.

14 MR. O'MALLEY: No objection.

15 THE COURT: Admitted.

16 MR. WONG: Thank you.

17 DIRECT EXAMINATION BY MR. WONG:

18 Q. Okay. Dr. Fruehauf, let's get right to your opinions.

19 In forming your opinions in this case have you reviewed  
20 the '219 patent?

21 A. Yes, I have.

22 Q. And have you reviewed the asserted claims of the '219  
23 patent?

24 A. Yes, I have.

25 Q. Let's see the '219 patent. It is DTX-0268. Let's go

—Direct - Fruehauf—

1 right to the claims on Page 11.

2 And, Dr. Fruehauf, in your opinion what is the subject  
3 matter of the '219 patent?

4 A. I think the subject matter of this patent is related to a  
5 formulation that maintains stability for 24 months of the  
6 compound, the active pharmaceutical ingredient, palonosetron.

7 Q. Okay. In your opinion who would a person of ordinary  
8 skill in the art be with respect to the '219 patent?

9 A. A formulator.

10 Q. Are you a formulator?

11 A. No. No, sir.

12 Q. What is your training in?

13 A. I'm a medical oncologist and a pharmacologist.

14 Q. Okay. So, how is that relevant to a POSA -- can I use  
15 the term "POSA" for a person of ordinary skill in the art?

16 A. Yes.

17 Q. How is your training relevant to a POSA for the '219  
18 patent?

19 A. Well, my expertise would be applied more to the  
20 administration to a human to reduce the likelihood of cancer  
21 chemotherapy-induced nausea and vomiting. Cancer  
22 chemotherapy-induced nausea and vomiting. And I'm trying to  
23 stick with mainly what's in the text there, but I do  
24 paraphrase, and I apologize.

25 THE COURT: Maybe if you slow down just a little bit.

—Direct - Fruehauf—

1 We have plenty of time.

2 THE WITNESS: Yes, ma'am.

3 BY MR. WONG:

4 Q. If we call that "CINV" is that okay?

5 A. Yes, sir.

6 Q. Okay. So, with respect to this part of the claim, what  
7 type of expertise are you offering for the '219 patent?

8 A. The clinical development component where how did they  
9 come to this conclusion that the drug is effective at reducing  
10 the risk of nausea and vomiting, and this is -- really the key  
11 is to reduce the likelihood of cancer chemotherapy-induced  
12 nausea, and that stems from the clinical trial data.

13 Q. Okay. Do you have preclinical and clinical expertise?

14 A. Yes, sir.

15 Q. Okay. Have you prepared a demonstrative to explain the  
16 various types of clinical trials?

17 A. Yes, I have.

18 Q. Okay. Let's have Fruehauf 2. Can you walk the Court  
19 through this general paradigm of preclinical and clinical  
20 trial processes?

21 A. So, this is an overview.

22 THE COURT: Just a second. Give me a moment. I'll  
23 be right with you. Okay. So, you have s demonstrative here.

24 Go right ahead.

25 THE WITNESS: So, this is an overview of the



—Direct - Fruehauf—

1 preclinical -- so that's before it gets to people -- and the  
2 clinical trial process. And, basically, this is what I  
3 discuss with my undergraduate students, but there's a  
4 preclinical phase. Somebody conceives of a drug or, you know,  
5 let's say a drug that would have an intended purpose to  
6 improve people's outcomes.

7           So, they have to test it in animals to show that it is  
8 safe in animals, and they'll have animal models that would be  
9 reproducing the human state that they're trying to mitigate.

10           So, for instance, they could use ferrets and give them  
11 high doses of chemotherapy like Cisplatin, and the ferrets  
12 would vomit. And they can then give the ferret the drug that  
13 they're developing that's supposed to suppress vomiting and  
14 show that at a certain dose for that animal, where the drug  
15 reaches a certain concentration in the animal's blood, it  
16 effectively suppresses the nausea.

17           So, that's the test of effective, and coming up with  
18 the dose in animals that's so critical to, you know, going to  
19 the FDA with this information of safety and efficacy to ask if  
20 we can give this to people. And the safety part is basically  
21 giving higher and higher doses of the drug to animals over an  
22 extended period of time and then sacrificing the animals and  
23 looking at all their organs through the microscope and  
24 checking their biology, their kidneys still function, is their  
25 liver fine, and so on and so forth.

—Direct - Fruehauf—

1           And, so, if you can find that at the doses needed to be  
2 effective in the animal model that it doesn't cause toxicity  
3 in the animal, then you go to the FDA and you file an  
4 Investigational New Drug Application. And that's this  
5 interface right here.

6           And when you go to the FDA with this information and  
7 you say, This is my plan in Phase I, I'm starting at a much  
8 lower dose than was found to be safe in the animal. I want to  
9 give a group of healthy volunteers this drug, and I'm going to  
10 give increasing amounts of the drug to make sure that as I go  
11 up and up and up in the doses that are given to people that I  
12 can cover the dose that I can, you know, predict was working  
13 in the animals.

14           So, I'll give a model dose that worked in animals to  
15 people in Phase I and find out if that's safe.

16           THE COURT: So, these folks are not suffering from  
17 nausea?

18           THE WITNESS: No, ma'am.

19           THE COURT: You're just checking for safety?

20           THE WITNESS: Yes. And when I was a medical student  
21 I would go in and work with the Phase I studies. These are  
22 usually younger people who are getting paid to come in for  
23 three days, and we give them the medicine, and we check their  
24 blood pressure and draw their blood and check their blood  
25 levels just to prove that in a normal human being there's no

—Direct - Fruehauf—

1 unexpected adverse event.

2 And, so, once we have gone up through this range of  
3 doses, and we have determined that it is not toxic and, also,  
4 that we have confirmed that we can give a dose in humans that  
5 are normal without an illness that matches the dose that was  
6 effective in animals, then we take these two pieces of  
7 information, we go back to the FDA and we say, Okay, we would  
8 now like to now prove that the drug is effective for the  
9 intended purpose on a group of patients, and that is the Phase  
10 II goal.

11 So, in Phase II of the trials we are determining if the  
12 dose we found is safe and is similar to the dose that was  
13 effective in animals will now be effective in humans.

14 And, you know, these study designs tend to be unblinded  
15 usually, and we would just give the drug to the people who are  
16 let's say cancer patients that are going to get chemotherapy  
17 that's highly nausea-provoking or highly emetogenic and see if  
18 the drug would prevent that nausea.

19 And if we have success here, in other words we have  
20 defined an effective dose in Phase II, then we go and ask the  
21 FDA, Do you agree that we have defined the effective dose,  
22 and, if so, can we take this into a larger Phase III trial  
23 where we can confirm in a larger group of people and do more  
24 safety analysis, and critically here in Phase III, compare the  
25 new drug with what's already out there that it would be

—Direct - Fruehauf—

1 equivalent or better than the existing therapies.

2           Then if these Phase III studies are effective -- it  
3 might just be one, two or three, it is not critical how many,  
4 but if your Phase III study is effective, then you go and ask  
5 for your New Drug Application approval so that you can  
6 commercialize the agent.

7           MR. WONG: Okay.

8           THE COURT: And you can select a couple of two or  
9 three different dosage levels to put into your Phase II or  
10 Phase III trials, right?

11           THE WITNESS: Absolutely. And I think that, you  
12 know, certainly in this case that's what was done.

13 BY MR. WONG:

14 Q. Okay. Now, Dr. Fruehauf, is this how drugs are currently  
15 tested for safety and efficacy?

16 A. Yes. This is the current process, and it goes back to  
17 the sixties when there was realization of the need for a sort  
18 of codified process that everyone could follow where, you  
19 know, these safety signals would be identified early and then  
20 that if you thought it was really working you could really  
21 prove that on a statistical basis.

22 Q. Okay. Now, who is carrying out these types of  
23 preclinical and clinical studies?

24 A. So, the preclinical studies would be done, you know, by  
25 scientists, pharmacologists, you know, Ph.D.s, and then --

—Direct - Fruehauf—

1 THE COURT: Ph.D.s in what?

2 THE WITNESS: Pharmacology, cell biology, physiology.

3 So, the preclinical work is mainly done by that level  
4 of person, and then when you go into people, of course, now  
5 we're talking about patients or even healthy volunteers, but  
6 if you're giving a drug to a person, you have to be a  
7 physician.

8 THE COURT: Yes.

9 THE WITNESS: So, that's where we start as clinicians  
10 in Phase I.

11 BY MR. WONG:

12 Q. Okay. By 2002 how would you characterize the practice of  
13 conducting these clinical trials?

14 A. Very routine.

15 Q. Okay. Now, going back to Phase II just to follow up on a  
16 couple of issues --

17 THE COURT: Do you design clinical trials? I know  
18 that you supervise them, right?

19 THE WITNESS: No, I have two INDs right now for two  
20 different clinical trials that I'm carrying out for melanoma.  
21 So, I have gone through this with the FDA.

22 THE COURT: The IND is where you go to get permission  
23 for Phase I research?

24 THE WITNESS: Well, actually, so the IND itself  
25 carries through all the way until you're done with Phase III.

—Direct - Fruehauf—

1 So you're making sort of amendments to your Investigational  
2 New Drug Application as you go forward.

3 BY MR. WONG:

4 Q. Okay. Were you in court on Tuesday to hear opening  
5 statements?

6 A. Yes, sir.

7 Q. Did you hear the term "minimum effective dose"?

8 A. Yes, I did.

9 Q. What is the minimum effective dose?

10 A. That would be the dose that has the sort of optimal  
11 effect for the intended purpose, such as, let's say,  
12 suppressing nausea, but is the least amount of drug because  
13 the more concentration you have in the blood, the more likely  
14 it is that the drug will bind to other places besides the  
15 intended target and give you side effects.

16 So, you want to avoid side effects as much as possible,  
17 so you want the minimum amount of drug that would have the  
18 intended effect.

19 Q. Okay. And in the clinical trials what does it mean that  
20 a trial is "randomized"?

21 A. So, randomized trials are trials where, you know, let's  
22 say there's different arms on a study. You know, for  
23 instance, the comparator study here, we have one arm that  
24 would be a standard drug that's already approved. Now we have  
25 the new drug.

—Direct - Fruehauf—

1           So, you might just have a two-arm study; one for the  
2 comparator, one for the new drug, which how do you know what  
3 the patient is going to get? You flip a coin or you use a  
4 random number generator. And then that patient would be  
5 randomly assigned to one of those two treatment arms. And  
6 that could go for four arms or three arms, it doesn't matter,  
7 but the simple thing would be you flip a coin. If it is three  
8 arms, you have a three-sided dice you throw in a sense, and it  
9 is just randomly picking.

10           So, this is to avoid bias. This is to avoid the  
11 physician sort of he wants the drug to work, let's say, or  
12 she, and, so, the doctor could subconsciously even put the  
13 better patient into a given arm. So, this is to avoid bias.

14 Q. Okay. What --

15           THE COURT: And if you have got -- you call it an  
16 "arm," which would be one substance being tested; another arm  
17 would be another substance being tested --

18           THE WITNESS: Yes, ma'am.

19           THE COURT: -- and this is probably blinded, so the  
20 doctor doesn't know which the doctor is administering, right?

21           THE WITNESS: Yes. The double-blinded --

22           THE COURT: We'll get there. I'm just -- arm, "arm"  
23 is your term for a given drug that's going to be administered.

24           THE WITNESS: Or a drug at a given dose.

25           THE COURT: Okay. Yes. But in randomizing you want

—Direct - Fruehauf—

1 to distribute your population, so you get about as many people  
2 in each arm.

3 THE WITNESS: Balanced.

4 THE COURT: Right? Okay.

5 BY MR. WONG:

6 Q. Okay. Your Honor, you mentioned "blinded."

7 Dr. Fruehauf, what does it mean when a trial is  
8 "blinded"?

9 A. So, the blinding would be, again, trying to avoid bias.  
10 And you don't want people to know, you know, what the patient  
11 is getting until after things are done so, there's not bias.

12 And, so, let's say you've got two drugs in a comparator  
13 study. One drug is given in a bag of 50 milliliters of  
14 solution through an I.V. The other drug is given as a quick  
15 bolus.

16 Now, obviously, how could you not let the person know  
17 if you just gave one or the other? So everybody gets the  
18 same. They'll get a placebo, let's say, in the bag and the  
19 active ingredient in the injection so that way nobody knows  
20 what that patient really got. And the blinding is there's a  
21 place where they put the drugs together with a number on it,  
22 and then they'll ship it based on the arm the patient is on,  
23 and only the people -- nobody really knows what they're  
24 getting.

25 Q. Okay.



—Direct - Fruehauf—

1 THE COURT: And double-blind?

2 THE WITNESS: So, the patient doesn't know and the  
3 doctor doesn't know and the company doesn't know.

4 BY MR. WONG:

5 Q. Okay. Just a little more glossary terms. In clinical  
6 trials, what does the term "first patient in date" mean?

7 A. So, you know, let's say you've got your IND and you're in  
8 Phase II and -- or you're in Phase III, and you have a  
9 protocol. So, the protocol has to go through a review by a  
10 review board, be approved, and once it's approved, the patient  
11 can be accrued to the study. They have to sign a consent.

12 THE COURT: Accrued?

13 THE WITNESS: Accrual is adding people into the  
14 study.

15 THE COURT: Fine. We just want to make sure that's  
16 the word you used.

17 THE WITNESS: Yes, ma'am. Thank you. I know it's  
18 like, to me, too much second nature.

19 So, "accrual" is a term just to put somebody into a  
20 trial, and once they have signed a consent, they can be  
21 randomized. And once they're treated, that's the first person  
22 on, so to speak.

23 Now, you can really consider once they sign the consent  
24 you intend to treat them, and that's -- they're the first  
25 person on.

—Direct - Fruehauf—

1 BY MR. WONG:

2 Q. And then on the other side, what does the term "last  
3 patient out date" mean?

4 A. So, that would be, you know, in the statistical design of  
5 the trial, you've made assumptions about what will happen,  
6 what the differences might be, and you have a number of  
7 patients that you think are required to be able to show what  
8 you want the study to show.

9 And, so, you have a target of end number of patients to  
10 be put on the study, and when you've reached that target,  
11 that's your last patient, you've met your accrual goal and  
12 that's the last patient on. And when they're last patient out  
13 is they got the drug, the effect of the drug was measured, and  
14 now they're done.

15 Q. As of the last patient out date in a clinical trial, what  
16 does the data look like?

17 A. So, in a blinded trial, the last patient out, you have  
18 all the data and all the results in your spreadsheet. You  
19 just don't know which patient got what drug.

20 Q. Okay. Is the data unblinded at some point?

21 A. So, once the last patient's out, there's sort of, you  
22 know, the term used in the pharmaceutical -- by companies is  
23 "cleaning" the data, so they have people that go and make sure  
24 all the data is correct, there aren't mistakes of, you know,  
25 this number should have been in this box or that box and so

—Direct - Fruehauf—

1 on.

2 So, they clean the data. And once it is cleaned, they  
3 lock the data.

4 Now, once you lock the data for the FDA, you can no  
5 longer change any of the data. That's it. It's fixed.

6 So, once the data is locked and can no longer be  
7 touched, then you can unblind the data, and now you'll know  
8 who got what and you can, you know, determine if the drug was  
9 effective or not.

10 Q. Okay. After the data is unblinded, can the data change  
11 at all?

12 A. No. It's been locked, so you can't change the data in  
13 any way.

14 Q. And in your experience in clinical trials, is the  
15 unblinding date important to investigators and sponsors of a  
16 clinical trial?

17 A. Absolutely. I mean, they've made an investment of  
18 millions of dollars. They want to help people. They want a  
19 compound that will do that. They want to know did this study  
20 show that the drug works. The physicians want to know.  
21 Everybody who participated wants to know.

22 Q. And when is the first analysis of the unblinded data  
23 typically done?

24 A. As soon as the unblinding is done then, you know, the  
25 clock is ticking. You want to get your results analyzed so

—Direct - Fruehauf—

1 that you can put together your NDA application if it's a Phase  
2 III study, or if it's the Phase II result, you want to go  
3 right away into Phase III.

4 THE COURT: So, but it's not just the -- you push a  
5 button on a computer and out comes the analysis, not quite?

6 THE WITNESS: It's pretty close to that. I mean, you  
7 have in the -- the clinical research -- the clinical --  
8 there's usually a company that's working for the drug company  
9 that handles the statistics, and they have the database. So,  
10 the database is set up to actually just be the input into the  
11 statistical analysis program.

12 And I've run these programs. I mean, it's not that  
13 complicated. So, it could take a couple of days to do an  
14 analysis once the data is unblinded.

15 BY MR. WONG:

16 Q. Okay. Is the initial statistical analysis of the  
17 efficacy data that is conducted -- that is conducted, the  
18 initial analysis, is that analysis reliable?

19 A. Well, the data never changed, and it's all preordained  
20 because when you go to the FDA and you say, I want to run a  
21 Phase III trial, for instance, you have to tell them what  
22 analysis you will do at the end, how you will do that  
23 analysis.

24 So, you have to follow what you already said you were  
25 going to do years earlier. So, that is it. That first

—Direct - Fruehauf—

1 analysis is the result of the study based on the preordained  
2 process of analysis.

3 THE COURT: Then why do you call it the first  
4 analysis? Can you go back and troubleshoot it?

5 THE WITNESS: You can't really change the data.

6 Now, what can happen, you know, I've been involved  
7 where, you know, we have the primary result and we have the  
8 analysis, but we notice something, let's say. We noticed  
9 that, gee, it seemed like people that had high blood pressure  
10 did better. So we can do what's called an ad hoc analysis of  
11 data, but that doesn't change the data. It's just another way  
12 of looking at the same data.

13 THE COURT: And saying, oh, and we also learned this  
14 in addition.

15 THE WITNESS: Correct. But for regulatory purposes,  
16 that wasn't preplanned, and so it isn't assigned the same  
17 degree of credibility.

18 MR. WONG: Okay. Thank you, Doctor.

19 THE COURT: And the analysis is not likely -- you  
20 know how if you do -- if you tell somebody to do a numerical  
21 computation of some sort and they do it and they bring it to  
22 you and you pick it up and you say this doesn't look right,  
23 then you find out that they made some mistake in the middle.

24 THE WITNESS: So, that you have avoided in the data  
25 cleaning step because this is so regulated.

—Direct - Fruehauf—

1 THE COURT: Regimented.

2 THE WITNESS: It's regimented. I mean, there's not  
3 room. I mean, I wouldn't say that mistakes are impossible,  
4 but there's a tremendous effort with lots of people who work  
5 through weekends and nights when this data is being cleaned to  
6 get to the result. There's tremendous stress on those people  
7 to get it right because if they don't get it right, they get  
8 their hand slapped by the FDA.

9 And, in fact, the FDA has stated that the way  
10 pharmaceutical companies do research is far superior to how,  
11 let's say, you know, a cancer center would do research because  
12 it's so regimented and refined as a process that's become so  
13 routine.

14 BY MR. WONG:

15 Q. Okay. Thank you, Dr. Fruehauf. Let's get back to your  
16 opinions in this case.

17 A. Yes, sir.

18 Q. As of the January 30th, 2002 date, was it known that  
19 administering palonosetron to humans reduces the likelihood of  
20 CINV?

21 MR. O'MALLEY: Objection; vague.

22 Known by whom?

23 Objection; vague. Objection as to form.

24 THE COURT: Can you rephrase?

25 MR. WONG: Sure.

—Direct - Fruehauf—

1 BY MR. WONG:

2 Q. With respect to a person of ordinary skills in the  
3 clinical sciences, would that person know as of January 30th,  
4 2002, that palonosetron administered to a human reduces the  
5 likelihood of CINV?

6 A. Yes.

7 Q. Okay. Have you reviewed the documents in this case that  
8 support your opinions?

9 A. Yes, I have.

10 Q. Have you prepared a summary of those documents?

11 A. Yes, I have.

12 Q. Let's go to Fruehauf 3.

13 Dr. Fruehauf, what were the key documents that showed  
14 that palonosetron reduced the likelihood of CINV by the  
15 critical date?

16 THE COURT: Counsel, before you allow the doctor to  
17 answer your question, are you asking him for documents that  
18 would be available to this hypothetical skilled artisan?

19 MR. WONG: That's right.

20 THE COURT: So, these are public by legal definition?

21 MR. WONG: Well, for the on-sale bar, it can be  
22 private documents, confidential documents, or public  
23 documents.

24 THE COURT: But available to the hypothetical skilled  
25 artisan --

—Direct - Fruehauf—

1 MR. WONG: Available --

2 THE COURT: -- I would think?

3 MR. WONG: Well, let me ask the doctor this.

4 BY MR. WONG:

5 Q. In your analysis of the question of whether a person  
6 would know if the palonosetron would work, what kind of  
7 documents did you review?

8 A. I reviewed the Phase II study results from the Syntex  
9 trial that was concluded in 1995.

10 THE COURT: And is that publicly available in 1995,  
11 Doctor?

12 THE WITNESS: No.

13 MR. WONG: I can ask.

14 BY MR. WONG:

15 Q. For your opinions herein today, did you review both  
16 public and private, confidential documents?

17 A. Yes, I did.

18 Q. Did you rely on both public and private, confidential  
19 documents in forming your opinions?

20 A. Yes, I did.

21 THE COURT: All right. You may proceed, but I want  
22 the distinction to be observed, if you would, please.

23 Is that your basis, Mr. O'Malley?

24 MR. O'MALLEY: Yes. He said, as you noted, quite  
25 clearly that this would be what a POSA knew. POSAs don't know



—Direct - Fruehauf—

1 our clinical -- our confidential clinical documents. There's  
2 no foundation for this slide.

3 THE COURT: Okay. So, we'll keep this distinction  
4 going, and you can ask your questions, Mr. Wong.

5 MR. WONG: Thank you.

6 BY MR. WONG:

7 Q. So out of the documents that you relied on, what were the  
8 key documents that formed your opinion?

9 A. So, I looked at the Syntex Phase II trial, 2330. That  
10 was the first study of palonosetron in people that were sick.  
11 And I looked at a meeting minutes that Helsinn had, where when  
12 Helsinn licensed from Roche who had acquired Syntex, Helsinn  
13 had a meeting with the Syntex folks to learn, well, what did  
14 we in-license? What's the science that we have now that we've  
15 in-licensed this? So, that meeting was in 1998.

16 And then after their review of this, they sent a letter  
17 to the FDA explaining their intentions for a clinical  
18 development program. That was November 1999. And then they  
19 began their Phase III studies and put out a press release to  
20 the effect that we are now carrying out a clinical trial based  
21 on results from the Phase II study. We've moved into Phase  
22 III.

23 And I reviewed the Phase III trials. I reviewed the  
24 reports for the trials and also a declaration by Cantoreggi  
25 who stated, you know, that they knew that the drug was

—Direct - Fruehauf—

1 effective at a certain time.

2 MR. WONG: Okay. Let's go right to the first  
3 document. Can we have the Syntex Phase II trials, DTX-0227.  
4 Let's go to Page 5 of the study.

5 BY MR. WONG:

6 Q. Dr. Fruehauf, do you recognize this document, DTX-0227?

7 A. Yes, sir. So, this is the final report on the 2330  
8 clinical trial, which is the dose ranging, efficacy, safety,  
9 and pharmacokinetic study of single-intravenous doses of  
10 RS-25259, which is palonosetron, for prevention of nausea and  
11 vomiting in chemotherapy-naïve cancer patients receiving  
12 highly emetogenic chemotherapy.

13 Q. Dr. Fruehauf, were you in court on Tuesday to hear Dr.  
14 Calderari's testimony on this document?

15 A. Yes, I was.

16 MR. O'MALLEY: And I'll just object until they lay  
17 the foundation that your Honor requested as to whether or not  
18 the POSA would have had this, since the overarching opinion is  
19 that a POSA would have known X.

20 THE COURT: Okay. Mr. Wong, can you -- is this  
21 available to a POSA?

22 BY MR. WONG:

23 Q. Would this document have been available to a POSA? Was  
24 this document publicly available as of 1995?

25 A. I don't believe so.

—Direct - Fruehauf—

1 Q. If you saw this document in 1995, would you understand  
2 that, and reviewing the data, would you understand that  
3 palonosetron was effective to reduce CINV?

4 MR. O'MALLEY: Objection. Calls for speculation.

5 THE COURT: Sustained.

6 You can ask him what this document tells him now.  
7 That's fine.

8 MR. WONG: That's fine.

9 So let's go to Page 14. Let's go right to results or  
10 the study synopsis, and let's go to objections down low. The  
11 objectives below.

12 BY MR. WONG:

13 Q. Dr. Fruehauf, what was a primary -- what was a primary  
14 objective of this Phase II study? Looking at this document  
15 today, what was the primary objective of the Phase II study?

16 A. It was, basically, to determine whether palonosetron,  
17 over a dose range of 1-90 micrograms per kilogram, given to  
18 patients who were treated with highly emetogenic chemotherapy  
19 would reduce the likelihood of chemotherapy-related nausea.

20 Q. Okay. In carrying out the primary objective of this  
21 study, would it include a determination of whether  
22 palonosetron reduces the likelihood of CINV when administered  
23 to humans?

24 A. Yes.

25 MR. WONG: Let's go to the methodology section.

—Direct - Fruehauf—

1 Right below.

2 BY MR. WONG:

3 Q. Dr. Fruehauf, how would you characterize this Phase II  
4 Study 2330?

5 A. This is a very strong Phase II study because it was  
6 randomized and double-blinded in multicenter, so in  
7 multicenter trials, you have a variety of people  
8 participating, which decreases bias.

9 And then it was this dose-ranging efficacy study, so  
10 they wanted to know what dose is working to suppress nausea.  
11 So it was a very strong design for a Phase II trial.

12 THE COURT: You said not all Phase II trials are even  
13 blinded at all.

14 THE WITNESS: Correct.

15 THE COURT: This was?

16 THE WITNESS: Yes.

17 MR. WONG: Okay. Let's go to the next section, the  
18 number of subjects section.

19 BY MR. WONG:

20 Q. Dr. Fruehauf, how many patients in total were involved in  
21 this Phase II Study, 2330?

22 A. There were 161 patients, more males than females, and  
23 then there were 13 patients who were excluded from the  
24 efficacy analysis for various reasons, which, you know, we  
25 won't go into, but -- and, so, it was 161 patients with 13

—Direct - Fruehauf—

1 excluded.

2 Q. And how many patients actually got the 0.25 milligram  
3 dose of palonosetron?

4 A. There were -- which is the equivalent of  
5 3-micrograms-per-kilogram dose. Of 3 micrograms per  
6 kilogram, .25 was the equivalent to 3 micrograms per kilogram,  
7 and there were 24 patients who received that dose.

8 Q. So, did the study design of this Phase II study allow the  
9 determination of whether palonosetron administered at  
10 0.25 milligrams reduces the likelihood of CINV when it was  
11 administered to a human?

12 A. Yes.

13 MR. WONG: Let's go to summary and conclusion section  
14 on Page 15.

15 BY MR. WONG:

16 Q. Right here in the first sentence, what was Syntex's  
17 conclusion on this Study 2330?

18 A. They concluded that all four doses, and they're talking  
19 about 3, 10, 30 and 90, they didn't -- .3 to 1 was a low dose  
20 that wasn't expected to have the full effect, but it did have  
21 some effect because no drug would have lead to, you know, zero  
22 control of nausea and vomiting.

23 So, they found that 3, 10, 30 and 90, let's take the  
24 percent complete control going across, those were equivalent  
25 and effective. All four doses were approximately equally

—Direct - Fruehauf—

1 effective as compared with the combined results from a cohort  
2 of the .3 to 1 micrograms per kilogram.

3 Q. And what do they state in the first sentence?

4 A. They state that palonosetron was administered as a single  
5 bolus intravenous injection of these doses 30 minutes prior to  
6 chemotherapy.

7 Q. So, let's focus in on the --

8 THE COURT: And that they were looking at suppressing  
9 CINV for 24 hours after the chemotherapy.

10 THE WITNESS: Yes, ma'am. So, the endpoints here  
11 were complete control at 24 hours, which means, by definition  
12 in the study, that they didn't throw up and they didn't feel  
13 nauseated. They didn't need a medicine to help them after  
14 they got the first medicine.

15 And then this is a second endpoint, complete response,  
16 where the numbers were a little lower because that would be  
17 those patients might have needed some rescue medicine, and  
18 then the median time --

19 THE COURT: What's the difference between complete  
20 control at 24 hours and complete response at 24 hours, can you  
21 tell us?

22 THE WITNESS: Yeah, this is really the difference  
23 between who needed a rescue medication, and the percentage of  
24 people -- like this is a lower number for complete response  
25 because they might have felt nauseated. They didn't throw up,

—Direct - Fruehauf—

1 but they might have felt nauseated. They filled out a  
2 questionnaire --

3 THE COURT: Yes.

4 THE WITNESS: -- about how they felt over the 24-hour  
5 period --

6 THE COURT: Yes.

7 THE WITNESS: -- and they used that questionnaire to  
8 assess the benefit of the drug for its intended effect.

9 THE COURT: And that last row says, "median time in  
10 hours to failure defined as first emetic episode or rescue  
11 drug."

12 THE WITNESS: Yes. So that is, you know, basically,  
13 they got the medicine, they got the chemotherapy, and how long  
14 did the medicine work for? When did it wear off?

15 So when it wore off, that means you're starting to feel  
16 sick. And that's the delayed emesis. And, so, let's say for  
17 the .25 or the 3-micrograms-per-kilogram, that time to failure  
18 was 22.7 hours, compared to, let's say, 19 for 10, greater  
19 than 24 for 30, and 21.8 for 90. We can see these numbers are  
20 all pretty consistent, but these numbers are lower, so there's  
21 sort of a --

22 THE COURT: In other words, the dosage beginning with  
23 3 and going up was pretty consistent. It's just the dosage  
24 below 3 that fell off.

25 THE WITNESS: So, you know, what we understand about

—Direct - Fruehauf—

1 palonosetron is it was very potent. And, you know, you're  
2 binding to a receptor, and if you -- if you have enough drug  
3 to bind to all the receptors and they're all blocked at a  
4 certain dose, giving more drug won't have any more benefit.

5 THE COURT: Doctor, we're talking about this H --

6 THE WITNESS: 5-HT.

7 THE COURT: -- 5-HT<sub>3</sub> receptor. That's not the only  
8 receptor that sends signals of nausea to the brain, is it?

9 THE WITNESS: No. As I was explaining earlier from  
10 my practice, I will combine drugs that will work on different  
11 receptors because here there's only a 50 percent control.

12 THE COURT: Even at best --

13 THE WITNESS: Even at best.

14 THE COURT: -- with palonosetron.

15 THE WITNESS: With one drug. So, if you give a  
16 second drug and a third drug, now you're going to improve your  
17 control rate to some degree; but, of course, as you add more  
18 drugs, you're getting into more side effects.

19 THE COURT: But the other drugs would target other  
20 receptors theoretically.

21 THE WITNESS: Correct.

22 THE COURT: Thank you.

23 THE WITNESS: So, here we have a saturation of the  
24 receptors, and as you go higher, you don't really see any  
25 change after that.



—Direct - Fruehauf—

1 BY MR. WONG:

2 Q. Let's just focus on the 0.25 milligram data that's under  
3 3-microgram-per-kilogram. What do the data, 46 percent,  
4 39 percent and 22.7 hours, based on those data what can you  
5 conclude about whether 0.25 milligrams of palonosetron reduced  
6 the likelihood of CINV in patients who got this dose?

7 A. It's very clear that it effectively reduced the risk. I  
8 mean, if there was zero here, from my clinical experience if  
9 you don't give any premedication to someone who's getting  
10 highly emetogenic chemotherapy, 90 percent of them are going  
11 to throw up.

12 THE COURT: Because that's nature's way --

13 THE WITNESS: That's nature's way.

14 THE COURT: -- is that right?

15 THE WITNESS: They get a poison, they want to throw  
16 up. So, you have to have something in there to suppress that  
17 natural reaction to the poison that we're putting in their  
18 veins.

19 And, so, this was partially effective, and then this  
20 was the maximal effect, I think, in this Phase II trial.

21 THE COURT: You're referring to the Column 3.

22 THE WITNESS: Yes.

23 THE COURT: The column under the Dosage 3.

24 THE WITNESS: Right. So this is -- these percentages  
25 of control are similar as they stated, all four doses were

—Direct - Fruehauf—

1 approximately equally effective. So these are all kind of the  
2 same. So this would be the minimal effective dose in this  
3 particular set of doses.

4 THE COURT: Referring to the column under 3.

5 THE WITNESS: Yes, ma'am.

6 THE COURT: When you use a pointer, the record, the  
7 cold page of the record, doesn't know which column, so I'm  
8 just filling that in for you. You don't have to worry about  
9 it.

10 THE WITNESS: Understood. Thank you. I'll try  
11 and --

12 MR. WONG: Thank you, your Honor.

13 Okay. Let's go back to the timeline, Fruehauf 3.

14 THE COURT: Okay.

15 MR. WONG: Unless you have any other questions.

16 THE COURT: I wonder, could we take a recess now?  
17 Would that be all right?

18 THE COURT: Back in session.

19 MR. WONG: Thank you, Your Honor.

20 BY MR. WONG:

21 Q. I think we left off on Fruehauf 3, the timeline.

22 Dr. Fruehauf, just wrapping up on the Syntex Phase III Study  
23 2330. What is the date of the study report, Study 2330? What  
24 is the date of the study report?

25 A. The date of the study report was July, 1995.

—Direct - Fruehauf—

1 Q. Now, if a person of skill in the clinical sciences were  
2 to see the data in the Syntex study, on or about 1995, would  
3 he or she come to the same conclusions that we just discussed?

4 MR. O'MALLEY: Objection, Your Honor. No foundation.  
5 We've already received testimony that that POSA could not have  
6 seen it.

7 MR. WONG: Your Honor, my question is just if that  
8 person were to see this document.

9 THE COURT: I'll permit it. Experts can be asked  
10 hypotheticals. I agree with you that there's not a fact upon  
11 which they could base this hypothetical, but I'll permit the  
12 question.

13 MR. LOMBARDI: Your Honor, at some -- maybe not now,  
14 but at some point it might be helpful to address the role of  
15 POSA in the ready-for-patenting analysis because it's  
16 different than the prior art and there's not a requirement  
17 that a person of skill in the art have seen the public data.

18 THE COURT: Okay. Let's defer that. Don't want to  
19 argue it now.

20 MR. WONG: Thank you.

21 THE COURT: Go ahead and make your record, Mr. Wong.

22 MR. WONG: Okay.

23 BY MR. WONG:

24 Q. The answer to my question was? Let me read the question  
25 again.

—Direct - Fruehauf—

1           If a person of skill in the art in the clinical  
2 sciences were to see the Syntex data as of 1995, would he or  
3 she come to the same conclusions that we just discussed?  
4 A. Yes, I think it would be clear that the drug at the .25  
5 milligram dose reduced the likelihood of nausea and vomiting.

6 Q. Okay. Let's move on.

7           What is the next document you considered in forming  
8 your opinions?

9 A. The July, 1998 Helsinn meeting minutes.

10 Q. And what is important about this document, this meeting  
11 minutes from July, 1998?

12 A. Well, this is really where Helsinn was taking the reins  
13 of the development process. And they needed to assess what  
14 they had, and this is really their interpretation of what the  
15 drug had done so far.

16 Q. Okay. Let's go to DTX-0015.

17           Okay. Let's orient ourselves. Is this the Helsinn  
18 meeting minutes that you relied on?

19 A. Yes, it is.

20 Q. Okay. And what is the title here of this document?

21 A. This is Helsinn Palonosetron Team Meetings,  
22 palonosetron --

23           THE COURT: These are all internal people?

24           THE WITNESS: So, these were -- yes, these were  
25 people from Syntex. There were some Syntex people --

—Direct - Fruehauf—

1 THE COURT: Okay.

2 THE WITNESS: -- and then there were -- no, they  
3 weren't all inside people. And then there were Helsinn  
4 people, and then there was an outside expert that was invited  
5 to the meeting.

6 THE COURT: They were paid to come by somebody?

7 THE WITNESS: I don't know. Probably.

8 THE COURT: Okay.

9 BY MR. WONG:

10 Q. Where were these meetings held?

11 A. In Palo Alto, California.

12 Q. And when did these meetings take place?

13 A. In July of 1998.

14 Q. Let's take a look, let's enlarge it and see who attended  
15 these meetings. So when you say outside consultants, what  
16 outside consultants attended the meeting?

17 A. A Dr. David Gandara from UC Davis.

18 Q. Do you know Dr. Gandara?

19 A. Yes, I do.

20 Q. Who is Dr. Gandara?

21 A. Dr. Gandara is a medical oncologist who has published  
22 widely on antiemetic chemotherapy trials, on chemotherapy for  
23 lung cancer. He's published more than 100 papers. His papers  
24 have been cited by more than -- each paper, might be a  
25 thousand people have cited his paper. So he's very well

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1 respected in the oncology community.

2 Q. Now, based on your review of these meeting minutes, what  
3 was the purpose of these meetings?

4 A. The purpose of the meeting, as I stated, was to  
5 understand on the -- from the perspective of Helsinn, what did  
6 Syntex do, what were their data, and how could we go forward  
7 in the regulatory process.

8 Q. Okay. Let's go to Page 8. This is DSC, Page 8. What  
9 does this -- if you blow it up a little bit more.

10 What does this portion of the -- in general, what does  
11 this portion of the meeting minutes disclose?

12 A. So, this discloses the doses that I'm pointing out here  
13 under the overview, where it states, "The following drug doses  
14 and concentrations are proposed for the CINV and PONV trials."  
15 So the chemotherapy-induced nausea and vomiting and  
16 postoperative nausea and vomiting trials.

17 And then below that, they have the CINV table, where  
18 they list a dose of drug that would be put in the 5 milliliter  
19 volume, with the concentration listed next to the dose, and  
20 the dose chosen for CINV was .25 -- or doses, .25, .75 and 2.

21 Q. What were these -- on what data were these doses chosen?  
22 Based on what data were these doses chosen?

23 A. The discussion at the meeting was about the Phase II  
24 trial, and based on the Phase II trial results, as we  
25 described, you're trying to identify in Phase II the minimally

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1 effective dose, and so they've taken that Phase II trial  
2 result and now they're proposing to take these doses forward  
3 into Phase III.

4 Q. Were all three doses actually studied in Helsinn's Phase  
5 III trials?

6 A. No, they reduced it down to .25 and .75, just those two.

7 Q. And just to be clear, as shown in this table for CINV,  
8 what was the concentration of the formulation where the dose  
9 was 0.25 milligrams?

10 A. The concentration was 0.05 milligrams per milliliter.

11 Q. And was the design of the Phase III clinical trials also  
12 discussed at these team meetings?

13 A. To some degree, yes.

14 Q. Let's go to Page 10. And let's -- first two paragraphs.  
15 This is DTX, Page 10, first two paragraphs. So under CINE  
16 study designs, what does Helsinn say about the Phase II  
17 studies?

18 THE COURT: We've already established that CINE is  
19 synonymous with CINV.

20 MR. WONG: Correct, Your Honor.

21 THE COURT: Do you see it that way, Doctor?

22 THE WITNESS: Yes, ma'am.

23 THE COURT: Okay.

24 THE WITNESS: Emesis or vomiting --

25 THE COURT: All right.

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1 THE WITNESS: -- are equivalent.

2 BY MR. WONG:

3 Q. So let me repeat the question.

4 What does Helsinn say here about Phase II studies?

5 A. It says that, you know, that they don't want to use a low  
6 dose because that wouldn't be ethical because it wouldn't have  
7 as much control, so they're proposing to test the effective  
8 doses seen in Phase II, and as we've stated, these were  
9 equivalent, according to the conclusion from the Phase II  
10 study. So we're going to take these equivalent doses in a  
11 sense and compare them to ondansetron at 32 milligrams which  
12 at that time was the standard dose for ondansetron to prevent  
13 chemotherapy-induced nausea and emesis.

14 THE COURT: Just saying this, ondansetron, 32  
15 milligrams, compared to a quarter milligram or three-quarter  
16 milligram of palonosetron.

17 THE WITNESS: Yes, ma'am. And this is because the --  
18 we use the term "potency," and so the mechanism of the drug is  
19 completely different. It doesn't compete with serotonin. So  
20 they have a receptor, serotonin would come and bind to the  
21 receptor. You can try and block that. Now you've got to have  
22 more of your drug than there are serotonin molecules to keep  
23 it from binding and signalling nausea.

24 But what palonosetron does is it binds a different  
25 place, and the receptor goes off the surface of the cell. And



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1 you don't have to compete with serotonin anymore because  
2 you've down-regulated the receptor completely. So this was a,  
3 you know, second-generation drug.

4 BY MR. WONG:

5 Q. Okay.

6 THE COURT: Palonosetron?

7 THE WITNESS: Yes, ma'am. Palonosetron was a  
8 second-generation 5-HT inhibitor.

9 BY MR. WONG:

10 Q. Just for the record, these -- these weighted doses of 3,  
11 10 and 30 micrograms per kilogram, what do they equal when you  
12 turn them into fixed doses?

13 A. .25, .75, and 2 milligrams.

14 Q. And what was the injection volume that Helsinn selected  
15 for these doses?

16 A. The volume is planned to be 5 milliliters.

17 Q. If a person of skill in the clinical sciences were to see  
18 this information, how would he or she interpret the  
19 information?

20 A. That Helsinn interpreted the Phase II trial results to  
21 indicate that the .25 milligram dose was the minimal effective  
22 dose, and they were going to take that with a couple of other  
23 doses that were higher into the Phase III study.

24 MR. WONG: Let's go to Page 12. If you could blow up  
25 the top section.

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1 BY MR. WONG:

2 Q. What is the title of this section of the meeting minutes?

3 A. This is entitled "Gandara Meeting."

4 Q. And with respect to the section, dose selection, what  
5 does it state regarding Dr. Gandara?

6 A. So, after meeting with Dr. Gandara and his review of the  
7 data, it states that the dose selection, and then we'll just  
8 quote what it says, "Gandara recommended that, despite the  
9 unusual result in 2332," which was an oral trial, not an I.V.  
10 trial, that the 3 microgram per kilogram was most likely the  
11 correct dose for chemotherapy-induced nausea and vomiting.

12 Q. Do you agree with Dr. Gandara's recommendation here?

13 A. Yes, I do.

14 Q. And why is that?

15 A. Because I think it's clear from the trial that the .25  
16 milligram dose was the inflexion point, and after that you've  
17 saturated the receptors and that that's the minimally  
18 effective dose and you want to avoid higher doses because, as  
19 you go up on doses, you're more likely to get side effects.  
20 So Dr. Gandara came to the same conclusion that I have, and  
21 he's recommending that he thinks that the 3 microgram per  
22 kilogram dose was most likely the correct dose for CINV.

23 THE COURT: For intravenous administration?

24 THE WITNESS: Yes, ma'am, for intravenous  
25 administration. Not for oral administration.

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1 BY MR. WONG:

2 Q. Let's go back to the timeline, Fruehauf 3. Dr. Fruehauf,  
3 what is the next document that you considered after the July,  
4 1998 meeting minutes?

5 A. I considered the 1999 Helsinn letter to the FDA.

6 Q. Were you in court when Dr. Calderari testified about this  
7 document?

8 A. Yes, sir.

9 Q. Okay. Let's go to the document DTX-0293. Just to remind  
10 the Court, what is this document, DTX-0293?

11 A. So, as we heard from Dr. Calderari, Helsinn could not  
12 directly communicate with the FDA because they did not have a  
13 subsidiary in the United States. So they had to hire a  
14 consulting firm to communicate on their behalf to the FDA. So  
15 the Austin, Texas, August Consulting Company was hired by  
16 Helsinn. And this is a letter to the Center for Drug  
17 Evaluation and Research at the FDA, where they are providing  
18 now on their INDs -- so they have licensed-in this IND which  
19 was already filed by Syntex, and they're amending it to go to  
20 the next step. Their proposal is now to go to three new Phase  
21 III protocols, PALO-99-03, PALO-99-04 and PALO-99-05.

22 Q. Did they actually attach the protocols to this letter?

23 A. Yes, sir.

24 MR. O'MALLEY: I'm sorry. I hate to interrupt. But,  
25 again, the foundational question we've been requesting as to

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1 all these documents and the Court has has not been  
2 established.

3 THE COURT: I think that's fine for you to note your  
4 objection when each document comes up, but we'll keep going.

5 MR. WONG: Let me repeat my question.

6 BY MR. WONG:

7 Q. Were the Phase III protocols, the proposed protocols,  
8 attached with this letter?

9 A. Yes, sir.

10 Q. Okay. Let's take a look at the protocols. Let's go to  
11 Page 21.

12 What is disclosed here?

13 A. So this is the 99-03 protocol which was basically  
14 addressing the question of single I.V. doses of palonosetron  
15 at the .25 and the .75. Now, they've, you know, just chosen  
16 these two, lower doses, versus ondansetron at a 32 milligram  
17 dose, in the prevention of moderately emetogenic  
18 chemotherapy-induced nausea and vomiting.

19 Q. Okay. And what is the date of this proposed protocol?

20 A. November 15th, 1999.

21 Q. Let's go to Page 34 in this document. And this is into  
22 the 99-03 proposed protocol. What is shown here at the bottom  
23 of Page 34?

24 A. So, what is shown here is, you know, they have to have  
25 the justification for the FDA on dose selection. They have to

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1 provide the data to the FDA for their protocol, and any  
2 investigator -- I mean, when I review protocols and I'm on our  
3 investigation, you know, IRB, Investigation Review Board, and  
4 I review maybe half of all the protocols that come through.  
5 And I want to know, well, should we open the study here, did  
6 the drug work? Has it been effective? I mean, could we  
7 expect a good result for our patients and our institution?

8 And so in the protocol, you need to be showing what the  
9 drugs did and why you picked, you know, this dose, for  
10 instance. And so they're just reiterating what we've already  
11 reviewed which was the Phase II data, to support their dose  
12 selection for the .25 milligram dose by giving the data from  
13 the Phase II study.

14 Q. And what does Helsinn say about this data on the next  
15 page?

16 THE COURT: Just a second. Doctor, the data in the  
17 table is the same as we saw.

18 THE WITNESS: Identical.

19 THE COURT: Right. The first column, the labels that  
20 they use are a little different.

21 THE WITNESS: Here, it's percent with CR, so complete  
22 response.

23 THE COURT: Complete response.

24 THE WITNESS: And then CC was the complete control,  
25 and then here was the time to failure where we saw, you know,

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1 the -- that number of hours it took before people actually got  
2 sick.

3 THE COURT: And what does this p-value refer to?

4 THE WITNESS: So the p-value is the probability that  
5 the result seen could have occurred by chance alone, and in a  
6 smaller trial like this where there's small numbers of people  
7 per arm, you know, you're really looking more for the trend  
8 or, as Dr. Calderari said, the signal. And so the probability  
9 that 46 percent control occurred by chance is one chance in 10  
10 that that occurred by a random event.

11 THE COURT: Okay.

12 THE WITNESS: And then this one says that there is  
13 one chance in a hundred that this time to failure occurred,  
14 you know, as a -- is a mistake.

15 THE COURT: So that's just a statistical explanation?

16 THE WITNESS: It's a statistical explanation, and the  
17 way I, you know, look at these data is that since these were  
18 pretty much equivalent, you can kind of combine all this and  
19 be -- you know, it's very clear that the drug reduced nausea  
20 and vomiting, and you could look at this number and say, gee,  
21 there was this statistically significant, even with these  
22 small numbers, delay in time to failure for the .25 dose.

23 BY MR. WONG:

24 Q. Okay. So let's go to the next page, and what does  
25 Helsinn say about this Phase II data on the next page? Let's

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1 blow up the first paragraph.

2 A. So, you know, as part of their protocol proposal to the  
3 FDA, again, they have to give the rationale for the dose  
4 selection. And so, they're saying that data from this Phase  
5 II study clearly demonstrate that the 3 microgram per kilogram  
6 dose or the .25 milligram dose of palonosetron is the minimal  
7 effective dose in preventing chemotherapy-induced nausea and  
8 vomiting.

9 Q. Okay. And do you agree with this statement to the FDA?

10 A. Yes, I do.

11 Q. Okay. Now, are you surprised that Helsinn is making this  
12 statement in this proposed protocol for its Phase III trial?

13 A. No, as I said, they need to have a statement about what  
14 the result was from Phase II. So Phase II, as we've said  
15 earlier, the goal is to find the minimally effective dose. So  
16 they're making the statement here that they did do that, they  
17 were successful in their Phase II trial, and that the  
18 minimally effective dose is the .25 milligram dose.

19 THE COURT: So they're building on their Phase II  
20 work?

21 THE WITNESS: Yes, ma'am.

22 BY MR. WONG:

23 Q. If a person of skill in the art in the clinical sciences  
24 were to see this statement to FDA, would they interpret the  
25 statement the same way?

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1 A. They would interpret this statement as to indicate that  
2 the Phase II study showed that the .25 milligram dose could  
3 reduce the risk of nausea and vomiting.

4 Q. Let's go back to the timeline, Fruehauf 3.

5 Dr. Fruehauf, what is the next document that you  
6 considered in forming your opinions?

7 A. The Helsinn press release.

8 Q. Let's go to DTX-1227. The Court has seen this document,  
9 but let's just orient the Court.

10 Were you in court when Dr. Calderari testified about  
11 this document?

12 A. Yes, sir.

13 Q. Is this the Helsinn press release that you're referring  
14 to?

15 A. Yes, it is.

16 Q. What is the date of this press release?

17 A. September, 2000.

18 Q. Was this press release public, made public as of  
19 September, 2000?

20 A. Yes, it was.

21 Q. Let's go to the third paragraph.

22 In the third paragraph, what does the public press  
23 release state about Helsinn's Phase II trials?

24 A. The public press release states, "The Phase II trials  
25 demonstrated the efficacy of palonosetron in the prevention of



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1 emesis with no significant side effects."

2 Q. Okay. If you read this press release as of September,  
3 2000, what would you understand about this disclosure?

4 A. I would understand that, you know, they were pleased with  
5 their results. They had accomplished what they wanted to in  
6 terms of they licensed the drug that had a successful Phase II  
7 trial as an underpinning of its further development and that  
8 palonosetron did reduce the risk of nausea and vomiting.

9 Q. Would a person of skill in the art in the clinical  
10 sciences understand that Helsinn knew that palonosetron  
11 reduced the likelihood of emesis?

12 A. Yes.

13 Q. Is it unusual for a company to issue a press release  
14 about their clinical trials?

15 MR. O'MALLEY: Objection, foundation.

16 THE COURT: I'll permit it.

17 BY MR. WONG:

18 Q. Based on your experience.

19 THE COURT: You read the public literature?

20 THE WITNESS: Yes, ma'am.

21 THE COURT: And a lot of other literature?

22 THE WITNESS: Yes, ma'am. I get --

23 THE COURT: Technical literature, you read also?

24 THE WITNESS: Yes, ma'am.

25 But I'll get e-mails, you know, like this not

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1 infrequently from clearinghouses that follow the press  
2 releases and then they send them to us so that we have -- are  
3 kept abreast of where drugs are in development because, of  
4 course, we're waiting for the next new thing for our patients.

5 And so -- and as the, you know, chief scientific  
6 officer Oncotech for -- for 14 years, we put out press  
7 releases, and we wanted to know -- you know, we wanted to let  
8 our clients know what we were doing and that we weren't just  
9 standing still, that we were making progress as a business.  
10 So I think that this is an example of a company that wants  
11 people to know that they are moving forward.

12 BY MR. WONG:

13 Q. For the record, this press release was issued by who?

14 A. Helsinn.

15 Q. Would a person of ordinary skill in the clinical sciences  
16 view the statements in this Helsinn press release differently  
17 had it been issued by a larger pharmaceutical company?

18 A. No, sir.

19 Q. And you actually reviewed the Phase III clinical trial  
20 reports?

21 A. Yes, sir.

22 Q. Okay. How many were there?

23 A. Three.

24 Q. Okay. And what were they called?

25 A. 99-03, to use shorthand, 99-04 and 99-05.

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1 Q. And, in general, what were the differences between the  
2 three Phase III study reports that Helsinn conducted?

3 THE COURT: That's in the record. We can move on.

4 MR. WONG: That's fine. Thank you, Your Honor.

5 BY MR. WONG:

6 Q. Let's look at the first study report, PALO-99-03,  
7 DTX-0288, and let's go to Page 3. Dr. Fruehauf -- you can  
8 blow up the entire -- thank you.

9 Dr. Fruehauf --

10 A. Yes, sir.

11 Q. -- do you recognize this document?

12 A. Yes, I do.

13 Q. Is this the final study report for 99-03?

14 A. Yes, it is.

15 Q. When was the study started?

16 A. The study was initiated with the first patient in in  
17 August 1st, 2000.

18 Q. And when was the study completed?

19 A. The last patient out was October 2nd, 2001.

20 Q. And when was the study report written?

21 A. This report was written July 19, 2002.

22 Q. Does the study report describe the batches -- does the  
23 study report describe the batches used in the clinical trial  
24 PALO-99-03?

25 A. Yes, it does.

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1 Q. Let's look at Page 7; let's go to the bottom section.

2 Dr. Fruehauf, what doses of palonosetron were  
3 administered in the 99-03 study?

4 A. You know, as we have stated previously, .25 and .75  
5 milligrams of palonosetron.

6 Q. And for the .25 milligram dose, what were the batch  
7 numbers?

8 A. The batch number -- the batch number for the .25  
9 milligram dose was 1737321 and HPA003.

10 Q. Okay. Does the study report provide the final efficacy  
11 analysis results?

12 A. Yes, sir.

13 Q. Let's go to Page 9 and under the summary section,  
14 efficacy results. Let's look at Table 1. What does Table 1  
15 report?

16 A. Table 1 reports that patients with a complete response  
17 rate during the first 24 hours after chemotherapy, which is  
18 the same endpoint as we looked at for the Phase II trial, and  
19 it shows that the -- for the zero- to 24-hour time period,  
20 that in this case, palonosetron at .25 had an 81 percent  
21 complete response rate.

22 Now, just -- this number is about double, you know,  
23 almost the prior number we looked at, and that's because this  
24 study looked at moderately emetogenic chemotherapy, whereas  
25 the Phase II study was done for highly emetogenic

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1 chemotherapy. So we would expect a higher number in this  
2 trial than in the Phase II trial.

3 Q. Does the data in Table 1 show that 0.25 milligrams of  
4 palonosetron reduces the likelihood of CINV when given to a  
5 human?

6 A. Yes, it does.

7 THE COURT: The likelihood --

8 MR. WONG -- of CINV.

9 THE COURT: Reduces it, yes.

10 MR. WONG: Right.

11 BY MR. WONG:

12 Q. Okay. And does the study report provide a plan for how  
13 the data was analyzed?

14 A. Yes, it does.

15 Q. Let's go to Page 56 of DTX-0288, in the bottom portion  
16 under 5.8.1. Dr. Fruehauf, how was the data analysis  
17 performed?

18 A. Well, the data analysis was performed according to the  
19 preplanned protocol. So before anybody went on this study, it  
20 was determined that this is what they would do. And then now  
21 the study is done and this is what they did, and they --

22 Q. How -- go ahead.

23 A. And they used a SAS software program which is a  
24 statistical analysis package. I used that in graduate school.  
25 I use a little more modern ones today, but the SAS company was

—Direct - Fruehauf—

1 the most common and widely accepted statistical package for  
2 running analysis, statistical analysis for clinical trials.

3 Q. Does the analysis plan indicate when the data was closed?

4 A. It states that the database was closed or locked on 19  
5 December, 2001.

6 Q. Does the statistical plan indicate when the database was  
7 unblinded?

8 A. It was unblinded on January 2nd, 2002.

9 Q. Did you review any initial analysis of the unblinded data  
10 from PALO-99-03?

11 A. Yes.

12 Q. And when was the initial analysis performed?

13 A. January 7th, 2002.

14 Q. Are you surprised that within a week of the unblinding  
15 dates, preliminary analysis of the data was performed?

16 A. No. As we discussed earlier, people want to know the  
17 answer. You know, if it's Christmas day and Christmas morning  
18 and you're eight years old and you're looking down under the  
19 tree, there's a package for you, you're not going to just sit  
20 there. You're going to run over there and open it. This was  
21 their first chance to see what were the results of this trial  
22 they've worked so hard to carry out.

23 Q. Analyzing the unblinded data?

24 A. Analyzing the unblinded data.

25 Q. Let's go to DTX-0264. Dr. Fruehauf, do you recognize

—Direct - Fruehauf—

1 this document?

2 A. Yes, I do.

3 Q. What is this document?

4 A. This is a document, again, August Consulting,  
5 representing Helsinn to -- it's a letter to the FDA, and it's  
6 a request for pre-NDA meeting, and that really means that they  
7 are putting their regulatory package submission in for  
8 licensure for the new drug application, and they're going to  
9 come in with their data to support that licensure.

10 Q. Okay. And what is the date of this letter?

11 A. The date of this letter is February 7th, 2002.

12 Q. Did you rely on this document in forming your opinions in  
13 this case?

14 A. Yes, sir.

15 Q. Was there anything attached to the letter?

16 A. Yes, there was.

17 Q. Okay. Let's go to Appendix 1, starting on Page 9. And  
18 if we can blow up the entire page on Page 9.

19 So, what was attached to the letter?

20 A. So, what we have here is the analysis of the unblinded  
21 data from the SAS output. And if we could blow up the bottom  
22 of the page here, down here, we can see it says, SAS, analysis  
23 tables, printed, 7 January, 2002. So this would be that SAS  
24 output, and then it further states that this is confidential  
25 property of Helsinn Healthcare S.A.

—Direct - Fruehauf—

1 Q. And what -- based on your experience, what does that  
2 indicate to you?

3 A. That indicates to me that these data were available for  
4 Helsinn's review on January 7th, 2002.

5 Q. In your experience, would you have expected that people  
6 at Helsinn would have seen this document on or about January  
7 7th, 2002?

8 A. In my experience, they would want to see it as soon as  
9 possible, yes.

10 Q. All right. Let's look at the data on Page 9. So let's  
11 just take the first row. That starts zero to 24 hours. What  
12 does the data look like for the 0.25 milligram dose?

13 A. The data for the .25 milligram dose in the first column,  
14 under treatment group, shows an 81 percent control, complete  
15 control -- complete response, not complete control, excuse  
16 me -- complete response, 81 percent complete response during  
17 the zero- to 24-hour period.

18 Q. Okay. If you saw this data on January 7th, 2002, what  
19 would you know about the efficacy of 0.25 milligrams of  
20 palonosetron to reduce the likelihood of CINV?

21 A. You would know that it did reduce the likelihood of  
22 chemotherapy-induced nausea and vomiting.

23 Q. And what does the 81 percent indicate again?

24 A. That 81 percent of the patients did not have nausea or  
25 vomiting during the first 24 hours -- pardon me?



—Direct - Fruehauf—

1 Q. Go ahead.

2 A. -- did not have nausea and vomiting in the first 24 hours  
3 after receiving that dose of palonosetron, 30 minutes prior to  
4 their chemotherapy.

5 Q. Have you compared this initial analysis of the data here  
6 to the analysis of data that was included in the final study  
7 report of PALO-99-03?

8 A. Yes, I have.

9 Q. Let's go to Fruehauf 4. Dr. Fruehauf, what is shown on  
10 the top portion of this document?

11 A. So the top portion of the slide is the SAS output table  
12 from the January 7, 2002, SAS run, you know, analyzing the  
13 data, the unblinded data.

14 Q. And what is shown on the bottom here, Fruehauf 4?

15 A. And this was the final report which of course, has the  
16 identical results.

17 Q. Is it surprising that the identical results in the final  
18 report are identical to the preliminary analysis?

19 A. They have to be because this was the, you know,  
20 pre-stipulated result of the unblinded data which had been  
21 locked so it can't change.

22 THE COURT: When was it locked?

23 THE WITNESS: It was locked before it was unblinded.

24 BY MR. WONG:

25 Q. All right. Let's go to Fruehauf 3 again, the timeline.

—Direct - Fruehauf—

1 And what was the date of the preliminary analysis?

2 A. January 7th, 2002, which occurred before the critical  
3 date.

4 Q. How does that inform your opinion overall?

5 A. That, you know, we have a clear understanding from a  
6 Phase II study that .25 was the minimal effective dose that  
7 was carried forward into Phase III, and in the Phase III  
8 trial, that .25 milligram dose was very effective at reducing  
9 the likelihood of chemotherapy-induced nausea and vomiting in  
10 a prospective randomized trial.

11 Q. Have you reviewed the other Phase III --

12 THE COURT: Why do you call it "prospective"? You  
13 used the word.

14 THE WITNESS: Yes, ma'am. Prospective is you plan it  
15 in advance, and you do what you plan to do, and you can't  
16 change what you plan to do.

17 BY MR. WONG:

18 Q. Have you reviewed the other Phase III reports in forming  
19 your opinions?

20 A. Yes, I have.

21 Q. Those would be 99-04 and 99-05?

22 A. Yes, sir.

23 Q. I don't want to go through all of them, but for the  
24 record, let's just look at DTX-0289 very quickly. Let's go to  
25 Page 2. Dr. Fruehauf, is this the study report for

—Direct - Fruehauf—

1 PALO-99-04?

2 A. Yes, sir.

3 Q. What was the start date of the study?

4 A. May 3rd, 2000.

5 Q. What was the finish date of the study?

6 A. December 27th, 2001.

7 Q. When was the study report written?

8 A. July 19, 2002.

9 Q. Okay. Let's go to DTX-0290, Page 2. Dr. Fruehauf, do  
10 you recognize this document?

11 A. Yes, I do.

12 Q. What is this document?

13 A. This is the PALO-99-05 clinical trial.

14 Q. When was the 99-05 clinical trial started?

15 A. First patient in was July 6, 2000.

16 Q. When was the last-patient-out date?

17 A. Last patient out was December 31, 2001.

18 Q. What was the date of the report?

19 A. The date of the report was August 2nd, 2002.

20 Q. Okay. Let's go back to the timeline, Fruehauf 3.

21 Dr. Fruehauf, have you reviewed any documents that --  
22 from Helsinn to the Patent Office that were helpful in forming  
23 your opinions?

24 A. Yes, I did.

25 Q. Okay. Let's see DTX-0287, Page 0413. Dr. Fruehauf, is

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1 this the document from Helsinn to the Patent Office that you  
2 were referring to?

3 A. Yes, it is.

4 Q. Let's start at the top. This declaration was submitted  
5 for what patent application number?

6 A. Patent Application Serial Number 11/129,839.

7 Q. And what was the title of the patent application?

8 A. The title was "Palonosetron for the treatment of  
9 chemotherapy-induced emesis."

10 Q. Was this application for one of the asserted patents in  
11 this case?

12 A. No.

13 Q. So why is it relevant to your opinions in this case?

14 A. Because this patent application states the date that the  
15 declarants say they knew that palonosetron was effective at  
16 reducing the risk of nausea and vomiting and that they knew  
17 that the .25 milligram dose could do that.

18 Q. Okay. Let's go to Paragraph 4. And who are the people  
19 that -- who are the declarants of this declaration?

20 A. Riccardo Braglia, Sergio Cantoreggi, and Enrico Braglia.

21 Q. Let's go to Paragraph 9. Do these paragraphs describe  
22 the role of each of the declarants?

23 A. Yes, it states here that Enrico Braglia and Riccardo  
24 Braglia worked with Dr. Macciocchi as he developed the  
25 clinical protocol of PALO-99-03, and they participated with

—Direct - Fruehauf—

1 Dr. Macciocchi in the design --

2 THE COURT: In the decision.

3 THE WITNESS: -- in the decision -- thank you,

4 ma'am -- in the decision to study palonosetron for the

5 treatment of acute and delayed-onset CINV and worked with him

6 to fund and implement PALO-99-03.

7 BY MR. WONG:

8 Q. Okay. Let's see Paragraph 10 below. What does Paragraph

9 10 state, Dr. Fruehauf?

10 A. It states that Sergio Cantoreggi also worked extensively

11 with PALO-99-03, was familiar with the work reported in

12 PALO-99-03.

13 Q. Did the declarants sign this declaration?

14 A. Yes, they did.

15 Q. Let's go to the last page, 416. On what date did each of

16 the three declarants sign this declaration?

17 A. August 23rd, 2010.

18 Q. Let's go back to the front, Paragraphs 2 and 3.

19 Dr. Fruehauf, please read what is stated here in these

20 paragraphs.

21 A. Paragraph 2 states, "We submit this declaration to

22 establish that Alberto Macciocchi, Enrico Braglia, and

23 Riccardo Braglia had conceived the invention defined by claim

24 1 of this application, and reduced it to practice, before

25 November 16, 2001, the date that Dr. Piraccini published

—Direct - Fruehauf—

1 abstract Number 5169 in Blood, Volume 98, Number 11, Part 2."

2 Q. Paragraph 3 as well?

3 A. Paragraph 3 states that "In particular, we submit this  
4 declaration to establish that Alberto Macciocchi, Enrico  
5 Braglia and Riccardo Braglia had conceived the idea to use  
6 palonosetron for the treatment of acute and delayed-onset  
7 CINV, and had conducted clinical trials in humans to test this  
8 idea, at least as early as October 2nd, 2001."

9 Q. Okay. Let's go to Paragraph 6 and 7. I apologize for  
10 jumping around. What do the declarants attach to this  
11 declaration?

12 A. They attach the clinical study report for PALO-99-03, and  
13 they state that, "As can be seen from Page 1 of Exhibit A,  
14 Helsinn initiated PALO-99-03 on August 1, 2000, and completed  
15 the study on October 2, 2001."

16 Q. Was Exhibit A the same PALO-99-03 report that we just  
17 reviewed?

18 A. Yes, sir.

19 Q. Let's go down to Paragraph 11. Let's look at the claim  
20 that was pending, and Paragraph 12, as well.

21 Dr. Fruehauf, what was the claim that was pending at  
22 the time of this declaration?

23 A. This claim states that "A method of treating chemotherapy  
24 or radiotherapy-induced acute and delayed emesis in an adult  
25 human for five days after an emesis-inducing chemotherapy or

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1 radiotherapy event, comprising administering to said human a  
2 single dose of a treatment-effective amount of about 0.25  
3 milligrams of palonosetron in the form of palonosetron  
4 hydrochloride prior to said emesis-inducing event, without  
5 administering any further palonosetron during said five-day  
6 period."

7 Q. And what do the declarants state in Paragraph 12?

8 A. And in Paragraph 12, they state that "Exhibit A proves  
9 that we had conceived each of the features of this method, and  
10 tested the method in humans, before October 2nd, 2001."

11 Q. What -- how are these paragraphs significant to you  
12 forming your opinions in this case?

13 A. Because it indicates that they're saying that they knew  
14 the result, they knew that .25 milligrams was effective to  
15 reduce the risk of chemotherapy-induced nausea and vomiting,  
16 by October 2nd, 2001.

17 Q. Let's go to Paragraph 17 and 18. What is described here  
18 in Paragraph 17 and 18 of the declaration?

19 A. This is further supporting their contention, "Thus, we  
20 had conceived the idea to use .25 milligram palonosetron for  
21 the treatment of acute and delayed-onset CINV, as described in  
22 claim 1, at least as early as August 1, 2001," which is the  
23 date that PALO-99-03 began.

24 And, "Mostly importantly, we had successfully tested  
25 the method in human patients, and we had done so before

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1 October 2nd, 2001 (the date the study was completed)."

2 Q. Dr. Fruehauf, in your experience, what does it mean when  
3 someone says, "We have successfully tested the method in human  
4 patients, and we had done so before October 2nd, 2001 (the  
5 date the study was completed)"?

6 A. In my experience, that would mean that they had some  
7 understanding of the result from the study and that it was  
8 successful.

9 Q. Okay. Now, as of --

10 THE COURT: Just a second. They did get the results  
11 of the study but not on October 2nd, right?

12 THE WITNESS: So they would have --

13 THE COURT: So what date are you relating to -- so  
14 what date are you relating to your answer here?

15 THE WITNESS: So this is --

16 THE COURT: Your answer was that in your experience,  
17 this sentence would mean that these inventors had some  
18 understanding of the result from the study and that it was  
19 successful. But your answer didn't give a date.

20 THE WITNESS: Before October 2nd, 2001.

21 BY MR. WONG:

22 Q. Okay. I can follow up with that. So as of October 2nd,  
23 2001, the last patient out date, the data was still blinded.  
24 Isn't that right?

25 A. Yes, sir.



—Direct - Fruehauf—

1 Q. Okay. How could investigators come to the conclusion --  
2 come to any conclusion on the study results when the data is  
3 still blinded?

4 A. So the data is constantly being reviewed, but it's always  
5 blinded. And in the protocol, it's stated that there were --  
6 there was an ethics committee that was reviewing the data and  
7 constantly analyzing what was happening, so you can know the  
8 blinded data, you can know the percentage of all the patients  
9 who had control of nausea and vomiting, but you wouldn't know  
10 what treatment they were getting.

11 Q. Okay. Have you prepared some slides to explain this to  
12 the Court?

13 A. Yes, I have.

14 Q. Okay. Let's go to --

15 THE COURT: The ethics committee includes Helsinn  
16 representatives?

17 THE WITNESS: Usually they're independent, and  
18 Helsinn had hired a German company to be the clinical research  
19 coordinator, and I think they picked an ethics committee. And  
20 it was stated in the protocol that there was this ethics  
21 committee, and they were receiving updates continuously. In  
22 the United States, we call it a Data Safety Monitoring Board.  
23 And we require, you know, I am first since I'm the chairman of  
24 our Data Safety Monitoring Board at UC Irvine. So we're  
25 always looking at any bad things that are happening to make a

—Direct - Fruehauf—

1 decision, should we stop that study. I mean, if people are  
2 getting really sick and there's not that much benefit, we  
3 should stop it.

4 BY MR. WONG:

5 Q. Okay.

6 THE COURT: But -- wait a minute.

7 Your -- that ethics board, ethics committee, are they  
8 working in secret, or are they allowed to tell the proponent  
9 of the study how it's going, if no adverse decisions have to  
10 be made?

11 THE WITNESS: So, in my experience in the United  
12 States, the pharma company will get a letter from the Data  
13 Safety Monitoring Board. The Data Safety Monitoring Board  
14 works in secret. It's confidential. They can actually see  
15 unblinded data, because they can monitor if the drug is  
16 hurting people.

17 THE COURT: Right.

18 THE WITNESS: And -- but what we see in our protocols  
19 is updates, where the DSMB sends a letter saying, we reviewed  
20 the safety, we agree the study can proceed. So they're not  
21 revealing anything other than there wasn't futility, because  
22 there is sometimes a futility that's reached where you're  
23 never going to prove the drug works.

24 That was not in this protocol. There was not a  
25 futility boundary described. But that is the concept that, if

—Direct - Fruehauf—

1 the drug is hurting people and it's never going to be shown to  
2 be effective, we should just turn it off. So that's one of  
3 the things that Data Safety Monitoring Boards review.

4 THE COURT: Well, you said two things. You said if  
5 it's hurting people, we definitely need to shut down this  
6 study, right?

7 THE WITNESS: Yes.

8 THE COURT: Then you said futility, it is not  
9 working, this thing, we can see from these early results of  
10 the Phase III that nothing's happening to help these patients.

11 THE WITNESS: That would be the ethical --

12 THE COURT: That would be futility?

13 THE WITNESS: Yes. That's the ethical principle that  
14 if it turned out that, you know, it wasn't working and people  
15 were throwing up 90 percent of the time --

16 THE COURT: No point in putting more of this into  
17 them?

18 THE WITNESS: Yes, ma'am.

19 THE COURT: Right?

20 THE WITNESS: Yes, ma'am.

21 THE COURT: Or putting more of it into more people?

22 THE WITNESS: Correct.

23 THE COURT: So even futility is reported back to the  
24 proponent of this study --

25 THE WITNESS: Well, they don't --

—Direct - Fruehauf—

1 THE COURT: -- sometimes?

2 THE WITNESS: Yeah. If it was -- but, you know,  
3 usually what you're seeing is, because it's all so routine,  
4 everything has pretty much been worked out carefully, you just  
5 get a letter back saying, we reviewed the study and everything  
6 looks good and continue.

7 MR. WONG: Let me ask a --

8 THE COURT: Steady as you go, in other words?

9 THE WITNESS: Yes, ma'am.

10 BY MR. WONG:

11 Q. Let me ask this question: As of October 2nd, 2001, the  
12 last patient out date, was blinded data available?

13 A. Yes.

14 Q. And could any analysis be performed on that blinded data  
15 as of October 2nd, 2001?

16 A. In my experience, yes.

17 Q. Could that analysis give any indication as to whether or  
18 not the drug was working?

19 A. Broadly, yes.

20 Q. Okay. Can you explain to the judge how that can be?  
21 Have you prepared some slides?

22 A. Yes, sir.

23 Q. Let's go to Fruehauf 5. Okay. What is here in Fruehauf  
24 5?

25 A. So these are the unblinded data, where we've already

—Direct - Fruehauf—

1 locked the database and we know who got what.

2 Q. And what can you -- what would the blinded data look  
3 like?

4 A. So you wouldn't know that 81, 73. You'd only know if you  
5 added all these up and averaged it, that would be the overall  
6 population control rate. And you could compare that, for  
7 instance, to a historical rate for, let's say, ondansetron.

8 Q. Okay. And let's go to the next slide. And when you  
9 compare the collected data for all three arms to the  
10 historical control rate, what are the outcomes that could --  
11 that could proceed?

12 A. There is three possible outcomes. So here would be a  
13 historical comparator like ondansetron that has an expected  
14 control rate, and then the blinded data which would include  
15 the comparator so it would include the two doses of  
16 palonosetron in the comparator. But it would be averaged, and  
17 if that average is low, that means the two drugs, in addition,  
18 were pulling down the benefit rate because they weren't  
19 working so the average is actually less. So the new drug was  
20 less effective than the comparator drug.

21 Q. What would the second outcome be?

22 A. The second would be where, in the next slide, we can see  
23 that the blue bar is the same height as the red bar, and it's  
24 equally effective. So when we average everything out, the  
25 comparator drug and the new drug, let's say, were equivalent

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1 in average to the historical comparator drug.

2 Q. And what is the third outcome that could happen?

3 A. And the third one would be where the new drugs are  
4 actually a little better than the comparator, and in the next  
5 slide, what we'll see is that the blue bar is higher because  
6 we're averaging the higher control rate from the new drugs  
7 with the comparator, and that gives us an advantage over just  
8 the comparator by itself.

9 Q. All right. As of October 2nd, 2001, the last patient out  
10 date, if you did this type of analysis on the blinded data  
11 from PALO-99-03, did you prepare a slide to show what that  
12 would look like?

13 A. Yes, sir.

14 Q. Let's go to the next slide.

15 Can you explain to the Court what the results would be,  
16 what is shown?

17 A. So, in the protocol, they had actually explained on Page  
18 64 that they had analyzed 7,000 patients who had been treated  
19 with antiemetic therapy and come up with a equation, a  
20 calculation, they could predict what a given patient, given a  
21 certain kind of chemotherapy, low, moderate or highly  
22 emetogenic, what ondansetron would do in terms of control rate  
23 in that setting. And they used a 70 percent historical  
24 efficacy control rate for ondansetron. And they needed to do  
25 that to sort of get a sense of how many people do we need to

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1 know that the new drug is going to be as good or better than  
2 ondansetron.

3 And if you average together these numbers which  
4 would -- what would be happening in a blinded setting, the  
5 blinded data is 74.4 percent compared to 70 percent, so, in my  
6 experience, you could reach a conclusion that the  
7 palonosetron .25 and .75 were reducing the risk of nausea and  
8 vomiting and maybe even a little more than the historical  
9 control.

10 THE COURT: Because they were pushing the  
11 ondansetron-only ratio up?

12 THE WITNESS: Correct.

13 THE COURT: They were exceeding the ondansetron-only  
14 ratio?

15 THE WITNESS: Yes, ma'am.

16 MR. WONG: Thank you.

17 BY MR. WONG:

18 Q. Now, how does that inform your opinions on the statements  
19 made in the Cantoreggi declaration?

20 A. This supports Cantoreggi's statement.

21 Q. Thank you.

22 Let's talk a little bit about the --

23 THE COURT: Just curiosity. The last patient out is  
24 what, October 2001, in the 03 study?

25 THE WITNESS: Yes, October 2nd, 2001.

—Direct - Fruehauf—

1 THE COURT: Right. So all that blind data is there.  
2 It hasn't gone through the cleanup, the quality control?

3 THE WITNESS: That's correct.

4 THE COURT: And it certainly hasn't been locked --

5 THE WITNESS: Yes, ma'am.

6 THE COURT: -- and then unblinded.

7 If I'm Helsinn and I wanted to take a peek as of  
8 October 3rd, 2001, just to the 99-03 results, can I do that?

9 THE WITNESS: This is the only thing you can do.

10 THE COURT: But I can do that much?

11 THE WITNESS: Yes.

12 THE COURT: What you've described here.

13 THE WITNESS: Because it's blinded so you're not  
14 compromising the data. The last patient's out. You're not  
15 going to change anything.

16 THE COURT: But you're allowed to see it?

17 THE WITNESS: Yes.

18 THE COURT: These gross figures?

19 THE WITNESS: Yes.

20 THE COURT: Gross blinded, not cleaned-up figures?

21 THE WITNESS: In my experience, that's true.

22 THE COURT: Okay.

23 MR. WONG: Thank you, Your Honor.

24 BY MR. WONG:

25 Q. Let's shift subjects.



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1 THE COURT: I thought possibly, for example, the  
2 consulting firm who does the -- for example, you're doing the  
3 Phase III clinical trial, Doctor, in your hospital, and you're  
4 doing it for a pharma company. Well, you know, what are they  
5 allowed to see of what you've got and when?

6 THE WITNESS: So, the CRO has the data.

7 THE COURT: CRO is the contract research  
8 organization.

9 THE WITNESS: Yes, ma'am. That's what they'd hired  
10 that, the German company, I can't remember their name, to  
11 collect the data, implement the study, collect the data. So  
12 they had the data. And they could ask for an analysis of  
13 blinded data because that's not precluded by the FDA.

14 THE COURT: Just a minute. You use the word "they."  
15 Are we talking about the German CRO company or Helsinn, the  
16 customer?

17 THE WITNESS: Helsinn could ask the German company to  
18 take a -- you know, do an analysis of the overall data. It's  
19 not compromised, it's not unblinded, and the study is done.

20 THE COURT: Okay.

21 BY MR. WONG:

22 Q. And just for the record, could -- as of October 2nd,  
23 2001, could a person of ordinary skill in the clinical  
24 sciences also conduct that same analysis on the blinded data?

25 A. Yes.

—Direct - Fruehauf—

1 THE COURT: If they could get ahold of the data?

2 THE WITNESS: Yes, ma'am.

3 BY MR. WONG:

4 Q. Let's talk about the formulations that were actually used  
5 in Phase II and Phase III trials. Have you performed a  
6 comparison of the formulations?

7 A. Yes.

8 Q. Let's go to Fruehauf 10. Let's walk through this. What  
9 is listed on the left side of the slide?

10 A. This is the Phase II formulation for the Phase II trial,  
11 and this is the Phase III formulation for the Phase III trial.

12 Q. Okay. And what is the active ingredient in each of the  
13 formulations?

14 A. The active pharmaceutical ingredient is identical,  
15 palonosetron .25 milligrams.

16 Q. And based on your review of the documents, was 0.25  
17 milligrams of palonosetron administered in the formulations  
18 for both the Phase II study and the Phase III study?

19 A. Yes.

20 Q. What -- let's stick with the Phase II formulation. What  
21 are the other components of the Phase II formulations?

22 A. These are inactive excipients that are just there to  
23 support, as we heard from testimony on Tuesday, just to  
24 maintain the tonicity, a buffer, water, they're inactive.  
25 They have no effect on the intended use.

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1 Palonosetron is the active ingredient. Once injected  
2 into a person, only palonosetron is going to mediate an effect  
3 to suppress nausea and vomiting. And these other things are  
4 just safe and they just get diluted in the blood.

5 Q. To be clear, do the inactive excipients, sodium  
6 chloride -- inactive excipients, sodium chloride, dibasic  
7 sodium phosphate, monobasic sodium phosphate --

8 THE COURT: Counsel, please. Slow down.

9 MR. WONG: -- water for injection. Thank you, Your  
10 Honor.

11 BY MR. WONG:

12 Q. -- water for injection, and NaOH solution, do they affect  
13 the efficacy of the 0.25 milligram dose of palonosetron?

14 MR. O'MALLEY: Objection, Your Honor. He said he has  
15 no expertise in formulation.

16 THE COURT: Does it go beyond his report?

17 MR. WONG: This is right in his report, and if I can  
18 lay a foundation.

19 THE COURT: Okay. Let's see.

20 BY MR. WONG:

21 Q. Dr. Fruehauf, are you a pharmacologist?

22 A. Yes, my Ph.D. is in pharmacology.

23 Q. Does a pharmacologist -- would a pharmacologist study the  
24 effects of the drug formulation when it's administered into  
25 the body?

—Direct - Fruehauf—

1 A. Yes. And, as a clinician, I want to know when I give the  
2 drug to someone that the things that are in that vial aren't  
3 going to do anything to interfere with the drug I'm giving to  
4 the patient. So, as a pharmacologist, I understand why  
5 they're there and what they're doing. As a clinician, I know  
6 they're not interfering with the intended effect of the drug.

7 Q. And what happens when the Phase II formulation is  
8 actually injected into the patient and into the blood?

9 A. It's the active ingredient by itself that's mediating the  
10 reduction in risk of nausea and vomiting.

11 THE COURT: Why do you use the word "mediating"?

12 THE WITNESS: It's a pharmacology term.

13 THE COURT: For --

14 THE WITNESS: It's just -- I'm sorry. You know, it  
15 carries out the effect or it carries out the activity or it  
16 carries the -- it is -- it's the business end. Without that,  
17 that's where the rubber meets the road. The other stuff is  
18 not on the road. Only palonosetron is carrying the car down  
19 the road.

20 BY MR. WONG:

21 Q. And would that be the same for the Phase III formulation?

22 A. Yes, sir.

23 Q. Do the inactive excipients listed in the Phase III  
24 formulation impact the efficacy of the 0.25 milligram dose of  
25 palonosetron when it is administered to the patient?

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1 A. No, they do not.

2 Q. If a person of ordinary skill in the clinical sciences  
3 understood that the Phase II formulation with 0.25 milligrams  
4 was effective for CINV, would that same person -- what would  
5 they understand about the Phase III formulation with that same  
6 0.25 milligram amount?

7 A. They would expect it to behave in an identical fashion.

8 Q. Let's go to Fruehauf 11. Let's go back to the '219  
9 patent.

10 THE COURT: May I just ask a quick question about  
11 this? I don't want to know much about pH. But pH buffering  
12 is something that the formulator always has to keep in mind  
13 and has -- somehow this is -- this multidisciplinary  
14 formulation process has to arrive at an appropriate pH --

15 THE WITNESS: Yes, ma'am.

16 THE COURT: -- for the formula that's involved.

17 THE WITNESS: Yes, ma'am.

18 THE COURT: Right? And then it's supposed to stay at  
19 that pH while it's in the bottle?

20 THE WITNESS: Yes, ma'am.

21 THE COURT: But once it's injected into the body, the  
22 body's pH --

23 THE WITNESS: Yes.

24 THE COURT: -- affects that, and we don't think about  
25 it anymore, for purposes of the problems we're talking about

—Direct - Fruehauf—

1 here.

2 THE WITNESS: Yes, ma'am.

3 THE COURT: But the pH in the bottle is important to  
4 the formulation?

5 THE WITNESS: It's more important to the injection  
6 process, because when it goes into the vein, it's now going to  
7 immediately interact with the cells of the vein.

8 THE COURT: And the blood inside the vein.

9 THE WITNESS: And the blood inside the vein. But the  
10 vein cells, the endothelial cells that make up the vein,  
11 they'll react with the excipients, and if the overall pH is  
12 acidic or basic, it would irritate. It wouldn't be balanced  
13 with the cells and the blood.

14 So you're trying to give a neutral -- the pH in the  
15 body is 7.4. So you're trying to design a solution that would  
16 be 7.4, so when you inject it into the body, it won't irritate  
17 the vein because that would be bad. And, you know, we -- and  
18 then what happens if it leaked out when it was being injected?  
19 Then it's in the tissue. And that can cause an extravasation  
20 is the term for -- extravasation is when things leak out, and  
21 that's a problem.

22 So you're trying to really have a balanced pH, balanced  
23 pH means around 7.4, so that when it goes into the body, it  
24 won't irritate.

25 THE COURT: Well, 5 is nowhere near 7.4, is it?

—Direct - Fruehauf—

1 THE WITNESS: Well, if we go back, I guess we could  
2 look at the formulation. So these --

3 THE COURT: Phase III is at 5.

4 THE WITNESS: Right.

5 THE COURT: Looks like Phase II --

6 THE WITNESS: This was 7.4. And then they're adding  
7 a sodium hydroxide which is basic and a hydrochloride to reach  
8 a pH of 5.

9 THE COURT: Excuse me just a minute, Doctor. Is the  
10 Phase II just saline?

11 THE WITNESS: No. It included a buffer, so the  
12 disodium -- dibasic sodium phosphate and monobasic sodium  
13 phosphate are buffers, in water, and then there was a --

14 THE COURT: So buffers to address pH?

15 THE WITNESS: Yes. And then the sodium hydroxide,  
16 hydrochloride are based in acid to give you a final pH of 7.4.  
17 Here --

18 THE COURT: So it was palonosetron, buffered for the  
19 pH to match the body's pH, and some saline water.

20 THE WITNESS: Yes.

21 THE COURT: Is that what it was in --

22 THE WITNESS: Yes, ma'am.

23 THE COURT: -- Phase II?

24 THE WITNESS: Yes, ma'am.

25 THE COURT: So then we go to Phase III, and there are

—Direct - Fruehauf—

1 some stabilizers in there, I'm told.

2 THE WITNESS: Yes. The --

3 THE COURT: Okay. We won't get to that right now.

4 THE WITNESS: Right.

5 THE COURT: But my only question is, we're getting  
6 buffering down to 5.0 --

7 THE WITNESS: They're bringing the pH --

8 THE COURT: -- give or take a little bit.

9 THE WITNESS: Yeah. They're bringing it to 5, which  
10 is somewhat basic, but when it reaches the blood, because that  
11 isn't like acid, it's not like hydrochloric acid, and it's  
12 buffered, it will immediately go to the body pH.

13 THE COURT: So 5.0 is okay for an intravenous --

14 THE WITNESS: Yes, it can be.

15 THE COURT: -- formulation of this? All right.

16 THE WITNESS: It can be, depending on all the other  
17 things that are there.

18 THE COURT: All right. Thank you.

19 MR. WONG: Thank you, Your Honor.

20 BY MR. WONG:

21 Q. Let's go to Fruehauf 11, and let's go back to the claims.

22 THE COURT: It was apropos of when you put this  
23 formula -- Phase III formulated I.V. vial product into the  
24 body, does it have any effect that's different in terms of  
25 therapeutic effect from what was injected into the body in



—Direct - Fruehauf—

1 Phase II? And my question was, well, does the buffering  
2 change the therapeutic effect at all, I guess?

3 THE WITNESS: And the purpose for this testimony is  
4 to say that, no, it has no impact on the active ingredient.  
5 But it's very important for other purposes.

6 THE COURT: Okay.

7 MR. WONG: Thank you, Your Honor.

8 BY MR. WONG:

9 Q. So let's go back to Claim 1 of the '219 patent and this  
10 clinical part of the claim that you opined on.

11 Dr. Fruehauf, considering all of the evidence we  
12 reviewed today, what is your opinion as to whether it was  
13 known prior to the critical date of January 30th, 2002,  
14 whether 0.25 milligrams was -- of palonosetron was -- could  
15 reduce the likelihood of CINV?

16 A. I think it would be clear to a person of skill in the  
17 clinical arts, based on the Syntex Phase II study, based on  
18 unblinded data analysis of PALO-99-03 where that output was  
19 January 7th and Cantoreggi's declaration that would  
20 potentially rely on blinded data, that it was clear that  
21 the .25 milligram dose reduced the likelihood of  
22 chemotherapy-induced nausea and vomiting.

23 Q. Thank you. We're almost done. Let's go back --

24 THE COURT: Before we get to the next whatever, line  
25 of questioning, I'd like to see counsel at the side for a

—Direct - Fruehauf—

1 moment on the record.

2 (The following occurred at sidebar.)

3 THE COURT: I don't have any earthshaking  
4 pronouncement at all, but the doctor's most recent answer was,  
5 it would be clear to a person skilled in the clinical arts  
6 that this dosage of the drug would be effective before the  
7 critical date.

8 Now, he started out his testimony saying, well, a POSA  
9 for this drug would be a formulator, not a clinical guy. And  
10 now the question is being asked as if the POSA is a clinical  
11 guy. And so I'm wondering whether -- I'm not saying that  
12 either the pending question or answer was improper. I'm just  
13 wondering whether at some point, if I'm being asked to define  
14 the POSA for purposes of this overall patent dispute, that the  
15 POSA for formulating the excipients that go into the drug  
16 might be a different POSA from a POSA evaluating the efficacy,  
17 potential efficacy of the active pharmaceutical ingredient in  
18 the formulation. And I leave that for you to think about.

19 MR. LOMBARDI: Just as a preview, Your Honor, we  
20 won't discuss it here, but this is something that has been  
21 played out through the case and through the definition of  
22 POSA, and the way the parties have dealt with the issue, and  
23 we can describe that for you now or just let things develop,  
24 but you're hitting on a point that is accurate and there is  
25 explanation for how this works.

—Direct - Fruehauf—

1           THE COURT: I'm taking a dim view of what you're  
2           telling me because in the trial briefs, I think one side or  
3           the other said, well, they say POSA is this, and we don't  
4           think that that's right, but it won't change the result in  
5           this case, so let's move on.

6           Well, sometimes, the definition of POSA does change the  
7           result in the case. And I just don't want to be blind-sided  
8           way down the road and have some of this testimony -- some of  
9           this testimony elicited by one or both sides, useless to me.

10          MR. WONG: If I can just add, I don't think there's  
11          any disagreement between the parties that the POSA does  
12          consult with others skilled in art, the POSA  
13          formulator, with others skilled in the art, including those --  
14          including those in the clinical sciences.

15          THE COURT: A POSA does consult with others of skill  
16          in the art -

17          MR. WONG: -- including those in clinical sciences.  
18          I don't think the parties dispute that.

19          MR. O'MALLEY: There is a dramatic disagreement among  
20          the parties regarding the POSA.

21          THE COURT: Okay, wait. We can't air this now. But  
22          before we let go of this witness or maybe even before we do  
23          cross, we are going to have to air it. So let's get through  
24          the direct, and then we'll have this discussion as best we  
25          can. And we won't have our experts in the room.

—Direct - Fruehauf—

1 MR. WONG: Okay.

2 THE COURT: And then I'll see where we go from here.

3 MR. WONG: Thank you. Five more minutes, at most.

4 THE COURT: No, no hurry. I'm glad that we at least  
5 are focused now.

6 MR. WONG: Thank you, Your Honor.

7 (Sidebar concluded.)

8 BY MR. WONG:

9 Q. Thank you.

10 Let's go back to the '219 patent, Page 1. Now,  
11 Dr. Fruehauf, do you have an understanding that plaintiffs'  
12 experts disagree with your opinion as to when it was known  
13 that palonosetron would reduce the likelihood of CINV?

14 A. Yes, I do.

15 Q. And what is your understanding of what plaintiffs'  
16 experts say?

17 A. Dr. Saab, who is a plaintiffs' expert, has said that he  
18 believes that you need two prospective randomized blinded  
19 trials.

20 THE COURT: Can you raise your voice just a little  
21 bit? Yeah, good.

22 THE WITNESS: Dr. Saab has stated that you would need  
23 two prospective randomized trials such as the Phase III trial  
24 here, two of those, to know that the dose reduced the  
25 likelihood of nausea and vomiting.

—Direct - Fruehauf—

1 THE COURT: The .25 dose?

2 THE WITNESS: The .25 dose reduced the risk or  
3 likelihood of nausea and vomiting from chemotherapy.

4 BY MR. WONG:

5 Q. And what is your opinion as to the standard Dr. Saab is  
6 applying to this inquiry?

7 A. I disagree because I think that one -- the FDA criteria  
8 and the Patent Office criteria are two different things. And  
9 I think a person of skill in the clinical sciences looks at  
10 these data and says, gosh, even just the Phase II study tells  
11 me that the .25 dose reduces the risk of nausea and vomiting,  
12 and then it's confirmed in the Phase III study that's  
13 prospective blind -- double-blinded and randomized. And, I  
14 mean, on the strength of those two studies alone, I think that  
15 it's clear that the .25 dose was effective at reducing the  
16 likelihood of cancer chemotherapy-induced nausea and vomiting.  
17 Q. Thank you.

18 Now, when was the data from all three clinical reports,  
19 all three clinical trials, when was that data completed and  
20 fully analyzed?

21 A. Sometime around August of 2002.

22 Q. And when was the '219 patent filed?

23 A. I believe it was January 30, 2003.

24 Q. So at the time Helsinn filed the patent, did Helsinn have  
25 the multiple Phase III clinical trial data that Dr. Saab is

—Direct - Fruehauf—

1 requiring?

2 A. Yes, they would have had the knowledge of all three Phase  
3 III studies, 99-03, 99-04, and 99-05.

4 THE COURT: As of January 30, 2003, when they file  
5 their patent application, is that what you understand, the  
6 question?

7 THE WITNESS: Before that time, in the summer before  
8 that -- in the summer of 2002, they knew that from those three  
9 trials. Then they filed January 30, 2003.

10 BY MR. WONG:

11 Q. Have you reviewed the patent specification for the '219  
12 patent?

13 A. Yes, I have.

14 Q. Does the patent specification include any of the  
15 completed and fully analyzed clinical trial data from PALO-03,  
16 PALO-04 or PALO-05?

17 A. No, it does not.

18 Q. Does the patent specification include any Phase I or  
19 Phase II clinical trial data?

20 A. No, it does not.

21 Q. Does the patent specification include any preclinical  
22 data?

23 A. No, it does not.

24 Q. Thank you, Dr. Fruehauf. No more questions.

25 THE COURT: So, at this point, you may step down.

—Direct - Fruehauf—

1 We're not finished with your testimony, but we're going to  
2 take a recess now, and I'll have a discussion with the lawyers  
3 before you're called back to the stand.

4 THE WITNESS: Okay. Yes, ma'am.

5 THE COURT: Okay. Thank you. Watch your step,  
6 please.

7 (Witness left the stand.)

8 THE COURT: Can I see you back at the side, counsel,  
9 on the record.

10 (The following occurred at sidebar.)

11 THE COURT: It's 10 of 12, and it's time for a  
12 recess. It's time for us to get some food in us, even though  
13 it's not like 12:30 or 1 yet. Off the record.

14 (Discussion held off the record.)

15 THE COURT: We are going to take a recess now. But  
16 when we come back after the recess, I think we need to have  
17 some oral argument directed to the issues, whatever they are,  
18 concerning the definition of the POSA. As I suggested, that  
19 there might be a problem that we need to address, at least  
20 preliminarily now, before we continue with the testimony of  
21 this first expert. Okay?

22 MR. WONG: Okay.

23 THE COURT: So I would like to see you back at --  
24 could we make it 1:00? Take a little extra long lunch? Will  
25 that work?

## —Colloquy—

1           RESPONSE: Yeah.

2           THE COURT: Okay. This won't be final argument, but  
3 I just need to know where we're going with this. Thank you.  
4 (Sidebar concluded.)

5           (Luncheon recess taken.)

6           THE COURT: Fine. Let's have whatever discussion  
7 necessary before we proceed with the testimony, and if it is  
8 appropriate, I think we should exclude our witnesses.

9           MR. O'MALLEY: We have done so, your Honor.

10          THE COURT: Okay.

11          MR. LOMBARDI: Both sides, your Honor.

12          Your Honor, I'll just start. I understood your  
13 question was on the definition of the person of ordinary skill  
14 in the art, and I don't think that there's really much of a  
15 dispute among the parties.

16          I'll give you kind of the general statement, and then  
17 I'll come back and show you specifics, but to give you the  
18 general idea, incorporated into both parties' definition of  
19 the person of ordinary skill in the art here is the idea that  
20 it is a person who is part of a team that -- that works for  
21 the formulation of a pharmaceutical compound.

22          And incorporated into both parties' definition is the  
23 idea that this person would collaborate with others of  
24 different expertises. And, so, the way both parties have  
25 approached this is that a person of ordinary skill in the art



—Colloquy—

1 is, in our case, we say a formulator who would have access to  
2 people in other areas, for instance, clinicians -- excuse me;  
3 I apologize, your Honor -- clinicians like Dr. Fruehauf to get  
4 information and to inform them in their evaluation of what has  
5 gone on.

6 And, so, that is what you see in the briefs.

7 DJ, if you could...

8 This is from our trial brief. Under level of ordinary  
9 skill in the art, Page 20. And we note that the  
10 patents-in-suit relate to the field of intravenous  
11 formulations of 5-HT<sub>3</sub> receptor antagonists, which your Honor  
12 has heard a lot about. "A POSA in that field is a formulator  
13 with a Ph.D. in pharmaceutical sciences, pharmaceutical  
14 chemistry, or a similar field involving pharmaceutical  
15 formulations."

16 And then this is the collaboration language: "The POSA  
17 would collaborate with persons of ordinary skill in the  
18 clinical sciences, for example, Ph.D. pharmacologists or  
19 practicing medical doctors with respect to issues regarding  
20 clinical safety and dose." So, there's the concept of the  
21 clinician, and that's the role that Dr. Fruehauf, obviously,  
22 is playing here.

23 Now, plaintiffs, it is a slightly different definition,  
24 but in this respect I believe is essentially identical. I'll  
25 show you this is from plaintiffs' trial brief in the section

## —Colloquy—

1 under obviousness, but this is where they talk about the  
2 definition of POSA.

3 THE COURT: Page what?

4 MR. LOMBARDI: It is Page 11. And, obviously, your  
5 Honor, the definition of POSA is the same for the entire case.  
6 It is the same for a patent. You have one POSA is the  
7 appropriate definition for POSA for that patent, and whatever  
8 issue comes up, the definition of a POSA stays the same.

9 If you had two dramatically different patents involving  
10 different expertise, you could have different POSAs, but for  
11 our case, there's just one POSA. And here's what they say the  
12 definition should be: "A person actively involved in the  
13 development of pharmaceutical products which involves a number  
14 of disciplines and requires collaborative teamwork amongst  
15 persons with relevant" expertise --

16 THE COURT: Experience.

17 MR. LOMBARDI: I'm sorry. -- "experience in  
18 designing and developing pharmaceutical drug product  
19 formulations that meet all regulatory requirements. As such,  
20 a POSA could have a degree in chemistry, pharmaceutical  
21 chemistry, pharmacy, medicine, clinical pharmacology, or  
22 another pharmaceutical science-related field and experience in  
23 designing, developing, evaluating, and/or testing  
24 pharmaceutical formulations." And then they talk about our  
25 definition.

—Colloquy—

1 Defendants' definition is similar, but it's limited to  
2 a formulator that collaborates with such medical  
3 professionals. Because the asserted claims are directed to,  
4 inter alia, treating emesis, however, a composite POSA  
5 definition that includes clinical expertise is appropriate to  
6 resolve the parties' obviousness dispute.

7 So, both parties talk about this idea that it's a team  
8 in which -- and as you see, we have different definitions  
9 about who the precise individual would be, but that individual  
10 would have access to others that were part of the team and  
11 would rely on others' expertise in their areas of expertise.

12 So, that's what -- that's what the definition of POSA  
13 is for purposes of this case, your Honor.

14 THE COURT: Would you excuse me? I'll be right back.

15 MR. LOMBARDI: Yes.

16 THE COURT: Right back.

17 (Brief recess.)

18 THE COURT: Okay. I'm looking at the one opinion,  
19 the one substantive opinion that we have filed in this case,  
20 which, as you know, had to do with the preamble language and  
21 whether it was limiting or not, and I didn't have to get into  
22 what a POSA was in that opinion.

23 But in the related case, you call it 502 -- 505(b)(2)  
24 case, Docket Number 12-2867 at Pages -- internal Pages 21 to  
25 23 we picked up a POSA definition that defendants' expert Dr.

—Colloquy—

1 Kibbe had supplied, and we had understood there was no dispute  
2 about it at that time.

3 So, with that, I'll hear from you, Mr. O'Malley.

4 MR. O'MALLEY: Sure.

5 Going to the claim construction decision you just cited  
6 to, our position was that the POSA dispute had no effect on  
7 your claim construction decision, and that's as far as we went  
8 on that and, truly, it didn't.

9 In this case, it's teed up, and while it may read  
10 similarly in some fashion, there's a meaningful difference  
11 between the two definitions.

12 As Mr. Lombardi indicated, our person of ordinary skill  
13 is a person actively involved in the development of a  
14 pharmaceutical product, which involves a number of  
15 disciplines, including clinicians. Their definition is a  
16 pharmaceutical formulator.

17 Now, that person works with persons in other  
18 disciplines, but I'm not aware of any decision that supported  
19 the invalidity of a patent based on how a work colleague would  
20 have interpreted the prior art to a POSA. And that's  
21 essentially the proofs you're going to be getting here.  
22 That's the proofs you got this morning.

23 Dr. Fruehauf doesn't claim to be a formulator, and he  
24 didn't interpret anything from the perspective of their POSA.

25 Now, what is this all about? It goes back to framing

—Colloquy—

1 the obviousness question. If you believe -- and you have  
2 already ruled, so it's curious that our opponent seems to  
3 still be in denial -- but if you acknowledge that this  
4 invention is about the treatment of emesis, which you've ruled  
5 is a meaningful claim limitation, then framing the obviousness  
6 question goes back to what would a POSA, including this  
7 clinician looking for a better treatment for emesis, where  
8 would he have started?

9 And if -- they have a problem with that because of all  
10 the facts we've alluded to in our opening, the NK-1s coming on  
11 the scene, et cetera, et cetera, et cetera. So, to try and  
12 push that aside they say, well, it is a formulator. And all  
13 he is going to be concerned about is making a more stable  
14 formulation of palonosetron. Everything else about what you  
15 pick as the active ingredient and so on, all that's out of his  
16 bailiwick. So, it's an attempt to sweep that more meaningful  
17 issue regarding the preamble language to the side.

18 Now, where that leaves them, though, I believe, is  
19 between a rock and a hard place. All the testimony you heard  
20 this morning and testimony you're going to hear about what one  
21 of ordinary skill would have done to pick a dose with respect  
22 to the dose limitation in our claims, either you're going to  
23 hear irrelevant testimony of what the POSA's work colleague  
24 would have done -- this clinician, not the POSA -- or you'll  
25 hear testimony from a formulator who never picks doses.

—Colloquy—

1 Either way, legally irrelevant.

2 So, I would submit it's a rather fundamental and  
3 important disagreement between the parties with respect to the  
4 POSA standard.

5 MR. LOMBARDI: And I don't know if you want to hear  
6 more about the legal consequences of this, but I do think it's  
7 very interesting to hear Mr. O'Malley articulate this. I  
8 don't think it's been articulated before, but I look forward  
9 to briefing this, because I think this shows why Mr. O'Malley  
10 can't have it both ways.

11 He wants, for purposes of claim construction, to make  
12 this an FDA-approved product. You have to have an  
13 FDA-approved product as part of it, but he wants it, also, to  
14 involve just a formulator because that's who he put on the  
15 witness stand was a formulator, was -- you heard from -- we  
16 just talked to him for two days -- Calderari, I'm sorry, was a  
17 formulator. But, anyhow, I can talk about what I believe are  
18 just rank inconsistencies in what --

19 THE COURT: He came along here as a fact witness.

20 MR. LOMBARDI: He did. But, your Honor, I would say  
21 what happened at Helsinn is indicative of exactly what both  
22 parties have said is going on with a person of skill in the  
23 art.

24 He was a chemist, a formulator, who dealt with others.  
25 He dealt with clinicians. He dealt with other scientists in

## —Colloquy—

1 informing his opinions on what he was going to do.

2 Now, I think you say that by analogy. I think that is  
3 similar to the situation in the real world with formulation  
4 and clinical approvals. You have teams. They deal together.  
5 They interact together.

6 So, somebody like Dr. Fruehauf could be talking to  
7 somebody like Dr. Calderari -- I can't believe I'm having  
8 trouble with that name already, Judge. I apologize.

9 THE COURT: It's going to get worse.

10 MR. LOMBARDI: I think it probably will be.

11 But you would have people like Dr. Fruehauf talking to  
12 chemical formulators. That's the way it works. I'm not aware  
13 of any case that says that you can't have that kind of POSA  
14 definition. In fact, we've seen it in other cases, and, your  
15 Honor, you probably referenced it in the DRL, the related  
16 case. I think your definition of POSA that you adopted there  
17 did make reference to the collaboration.

18 THE COURT: It was yours.

19 MR. LOMBARDI: Yes. Well, not mine. We weren't  
20 there, but DRL's. But it is included in the definition.

21 But the bottom line here is that a POSA includes this  
22 collaborative effort. And, so, the collaborative effort means  
23 that a formulator would be -- talk to a clinician about what  
24 the meaning of the trials meant. The clinician would be  
25 talking to the formulator about stability issues --

## —Colloquy—

1 THE COURT: You're repeating, I know.

2 MR. LOMBARDI: Okay. So, I'm sorry. I'll stop. And  
3 I will save for later what I think are very problematic  
4 inconsistencies in plaintiffs' position, but that I think is  
5 probably better dealt with on briefing.

6 THE COURT: I'm not going to rule on it right now  
7 anyway.

8 MR. LOMBARDI: Okay. But that, I think, that's our  
9 position.

10 THE COURT: I see.

11 MR. O'MALLEY: I just want to correct something Mr.  
12 Lombardi said. He said, well, we put a formulator up; but  
13 letting aside your accurate observation, he was a fact  
14 witness, the difference is our definition is broader. It  
15 includes anyone involved in the development of pharmaceutical  
16 products, a multidisciplinary team. That's the only -- that's  
17 the only POSA who can develop a new drug product.

18 You need a formulator. You need a clinician. Dr.  
19 Fruehauf is a person of ordinary skill under our definition.  
20 He is not under theirs. So, there's no contradiction. Our  
21 definition is simply broader.

22 And, again, it gets back to the point of the preamble  
23 and is it meaningful? And if it's meaningful, how in the  
24 world is a formulator alone going to develop this new  
25 treatment for emesis?



## —Colloquy—

1 MR. LOMBARDI: And, your Honor --

2 THE COURT: No.

3 MR. LOMBARDI: No?

4 THE COURT: No.

5 MR. LOMBARDI: Okay.

6 THE COURT: Okay. From there.

7 MR. LOMBARDI: Okay. From there.

8 We are not trying to pigeonhole this into just a  
9 formulator. As counsel knows, we are calling -- he referenced  
10 specifically the obviousness inquiry. You'll hear from a  
11 formulator, and you'll also hear from a clinician on our side  
12 on obviousness.

13 And on the preamble, we are not ignoring the preamble  
14 at all. We're trying to keep -- we understand exactly what  
15 your Honor's ruling was, and we're conforming to that ruling  
16 and we're making our proofs conform to that ruling.

17 What we're objecting to, as I think your Honor has  
18 probably picked up, is the idea that that ruling indicates  
19 that FDA approval is somehow incorporated into the claim terms  
20 of the patent, which we say there's absolutely no support for.  
21 And that's our position.

22 THE COURT: Okay. This has been a useful discussion.  
23 I don't have any trouble hearing, so far, the expert testimony  
24 that I've heard couched in terms of whoever is speaking within  
25 the range of their expertise. Later we'll figure out who this

—Fruehauf - Cross—

1 hypothetical construct person of ordinary skill regarding  
2 these patents is, and I don't think that we are losing the  
3 benefit of going forward with testimony now with each of these  
4 experts.

5           If they render an opinion as they do from the  
6 standpoint of a POSA, you can incorporate your definition of  
7 POSA and have it in front of them, and I will understand that  
8 they are speaking from the definition of POSA that the party  
9 bringing the witness is proposing. I think that's the best I  
10 can do right now.

11           MR. O'MALLEY: Thank you.

12           THE COURT: Okay. So, you can put it on an index  
13 card. Put it up here with your expert, and you can state for  
14 the record at that time that you're incorporating by reference  
15 your proposed definition.

16           Will that at least get us moving forward?

17           MR. LOMBARDI: No problem from our point of view.

18           MR. O'MALLEY: Yes, your Honor.

19           THE COURT: Okay. Good.

20           MR. LOMBARDI: Should we bring the witness back into  
21 the room, your Honor?

22           THE COURT: Sure.

23           MR. LOMBARDI: Okay.

24           MR. O'MALLEY: I have a book of exhibits for the  
25 witness.

—Fruehauf - Cross—

1 THE COURT: Okay. Fine.

2 MR. O'MALLEY: And the exhibits we use will be in the  
3 books, but they'll also appear on the screen, whichever is  
4 easier.

5 THE WITNESS: Okay. Thank you.

6 I can do that. Thank you so much.

7 CROSS-EXAMINATION BY MR. O'MALLEY:

8 Q. Dr. Fruehauf, you've been retained by Teva in this case  
9 to offer opinions as to how a person of ordinary skill in the  
10 art in clinical sciences would have interpreted various  
11 information; is that correct?

12 A. Yes, sir.

13 Q. Now, Dr. Fruehauf, you finished your fellowship in  
14 oncology in 1992; is that correct?

15 A. Yes, sir.

16 Q. And since 1992, you've been at UC, Irvine where you've  
17 been involved in laboratory and clinical research; is that  
18 correct?

19 A. Approximately.

20 Q. In the two decades since then, you've only been involved  
21 in one clinical trial, I believe you told me, involving  
22 antiemetics; is that correct?

23 A. Yes.

24 Q. And that clinical trial, I believe you testified, was so  
25 long ago you do not remember the details; is that correct?

—Fruehauf - Cross—

1 A. True.

2 Q. But, in any event, that antiemetic trial did not result  
3 in an FDA-approved drug; correct?

4 A. No, it did not.

5 Q. And in the two decades that you've been at UC, Irvine,  
6 you've only worked on two or three trials that resulted in  
7 FDA-approved methods of treatment, correct?

8 A. Yes.

9 Q. And those trials did not involve antiemetics, correct?

10 A. No.

11 THE COURT: Correct? Yes?

12 BY MR. O'MALLEY:

13 Q. No, it's not correct?

14 A. No, they did not involve antiemetics.

15 Q. Okay. Thank you.

16 In fact, the emphasis of your research efforts has not  
17 been on research or clinical trials that will get a drug  
18 approved, correct?

19 A. No, that's not correct.

20 Q. So, you say that the emphasis isn't so much to work on a  
21 drug that will get approved --

22 THE COURT: You're talking emphasis? Emphasis.

23 BY MR. O'MALLEY:

24 Q. Emphasis.

25 So, it's your testimony today that the emphasis of your

—Fruehauf - Cross—

1 research hasn't been so much to work on a drug that will be  
2 approved because that's what big companies do. That's not  
3 your testimony today?

4 A. I don't think I gave that testimony today. I'm happy to  
5 try and --

6 Q. Is that accurate? Yes or no?

7 A. No.

8 Q. Okay. Let me show you your deposition transcript.

9 A. Thank you.

10 MR. O'MALLEY: And, Roy, if you can give me Page 18,  
11 Line 24 to 20, Line 6.

12 BY MR. O'MALLEY:

13 Q. Okay. So, the question was: "It could be participation  
14 in Phase II trials that eventually lead to an approved method  
15 of treatment by the FDA. So, with that understanding, are  
16 there any others beyond the Votrient®" -- and you understand  
17 the context was regarding clinical trials that lead to an  
18 FDA-approved method of treatment; you understand the context  
19 of that question?

20 A. Yes, sir.

21 Q. And then I'll read the full answer for the sake of the  
22 record: "Well, I guess the GOG trial on Avastin®, that was  
23 the Phase II study of Avastin®. I participated in the  
24 translational endpoints for evaluating markers that would  
25 predict response to Avastin® in ovarian cancer and then

—Fruehauf - Cross—

1 subsequently, it has been approved now for ovarian cancer.  
2 I'm, you know, working on the biomarkers for cervical cancer.  
3 It was just approved for cervical cancer, and I'm  
4 participating in an R21 grant study on markers linked to  
5 treatment response in cervical cancer.

6 "But the emphasis for investigators in the university  
7 setting at a comprehensive cancer center where I am, the  
8 emphasis is not to do the pharmaceutical company trials as  
9 much as it is to develop your own trials and do your own  
10 investigations because the NCI values that. And when you  
11 receive the large grant from the NCI -- there's 30, 31  
12 comprehensive cancer centers in the United States -- and, so,  
13 to maintain our standing and our grant, the emphasis for our  
14 faculty who do investigational clinical trials is to do  
15 hypothesis-driven investigational trials rather than the large  
16 pharmaceutical trials or to do cooperative group trials.

17 So, the emphasis isn't so much to work on a drug that  
18 will get approved because that's what big companies do."

19 Did I read that correctly?

20 THE COURT: Read the last sentence. You misread it.

21 BY MR. O'MALLEY:

22 Q. Oh, I'm sorry.

23 "So, the emphasis isn't so much to work on a drug that  
24 will get approved because that's what big drug companies do."

25 Did I read that correctly?

—Fruehauf - Cross—

1 A. You read that correctly.

2 THE COURT: Sir, Doctor, what does NCI stand for  
3 there?

4 THE WITNESS: National Cancer Institute.

5 THE COURT: And that's where the grants come from?  
6 These grants you're talking about here.

7 THE WITNESS: These grants come from the National  
8 Cancer Institute, and so for promotion in the cancer center  
9 program, we're asked to do, to come up with our own ideas for  
10 clinical trials; but we still have to do all of the other  
11 Phase III trials that we're involved in. So the emphasis  
12 academically is what I was talking about.

13 THE COURT: Okay. Let me ask the questions.

14 THE WITNESS: Oh, I'm sorry.

15 THE COURT: I was just looking for what the  
16 abbreviation was.

17 THE WITNESS: Yes, ma'am.

18 BY MR. O'MALLEY:

19 Q. So the emphasis of your research efforts has not been on  
20 selection of an efficacious dose for a drug to obtain FDA  
21 approval, correct?

22 A. No, that's not correct.

23 Q. Well, in fact, you've never been personally involved in  
24 the selection of a specific dosage of a drug in a treatment  
25 that was eventually approved by the FDA, correct?

—Fruehauf - Cross—

1 A. And you asked me that during my deposition, and I was  
2 explaining that as clinicians, we are involved --

3 Q. Sir, can you answer that yes or no? It is a simple  
4 yes-or-no question.

5 A. Okay. I wouldn't be the only one involved in choosing  
6 the dose, that's correct.

7 Q. No, the question is: In fact, you've never been  
8 personally involved in the selection of a specific dosage of a  
9 drug in a treatment that was eventually approved by the FDA,  
10 correct?

11 A. I'll say yes.

12 Q. Yes, you've never been personally involved?

13 I'm just trying to see what your "yes" is. Is that --  
14 did I interpret that correctly?

15 A. Well, it depends on the definition of "personally  
16 involved", but --

17 Q. Is that what you meant by your "yes"? That's simply the  
18 question.

19 A. Yes, that's what I meant by my yes.

20 Q. Okay. Thank you.

21 Now, have you ever done a formal pharmacology research  
22 fellowship?

23 A. My Ph.D. is in pharmacology. There's no fellowship  
24 associated with that.

25 Q. You've never done a formal pharmacology research



—Fruehauf - Cross—

1 fellowship; correct?

2 THE COURT: Is there such a thing? Are you assuming  
3 there is such a thing?

4 MR. O'MALLEY: I know there to be such a thing, your  
5 Honor.

6 THE WITNESS: I did receive a fellowship grant during  
7 my Ph.D. in pharmacology at Rush.

8 BY MR. O'MALLEY:

9 Q. Was that what you would consider a formal pharmacology  
10 research fellowship?

11 A. Research fellowship, yes.

12 Q. Are you associated with the American Society of Clinical  
13 Pharmacology and Therapeutics?

14 A. Not at this time.

15 Q. Are you associated with the American College of Clinical  
16 Pharmacology?

17 A. No.

18 Q. Are you board certified in clinical pharmacology?

19 A. No.

20 Q. Now, I believe you testified that you're not a  
21 pharmaceutical formulator, correct?

22 A. Correct.

23 Q. And you understand Teva's definition of a person of  
24 ordinary skill, correct?

25 A. I'm not sure at this time.

—Fruehauf - Cross—

1 Q. Do you understand that it's a pharmaceutical formulator?

2 A. I believe that's true.

3 Q. And that's not you, correct?

4 A. Correct.

5 Q. However, because the '219 patent involves a method of  
6 treating CINV with a specific dosage of palonosetron --

7 THE COURT: It's actually a compound, not a method  
8 patent, counsel, right?

9 MR. O'MALLEY: Okay.

10 THE COURT: A composition patent?

11 BY MR. O'MALLEY:

12 Q. Okay. However, because the '219 patent has a preamble  
13 involving treatment of CINV with a specific dosage of  
14 palonosetron, then evaluating that limitation of the patent  
15 claims would bring in the experience of a clinician, right?

16 A. Yes, sir.

17 Q. Now, you gave an opinion as to written description. Do  
18 you understand what I mean by "written description"?

19 THE COURT: In your expert report, not here.

20 THE WITNESS: Yes.

21 BY MR. O'MALLEY:

22 Q. Well, do you understand that the testimony at the end of  
23 your testimony today related to the issue of written  
24 description?

25 A. I understand that.

—Fruehauf - Cross—

1 Q. Okay. In fact, you presented opinions that our patent  
2 claims are invalid for lack of written description in your  
3 expert report, correct?

4 A. Yes, sir.

5 Q. Now, you signed an expert report in this case on  
6 August 15, 2014; is that correct?

7 A. I believe that's correct.

8 Q. And that expert report accurately reflects the opinions  
9 you gave in court earlier today, correct?

10 A. I believe so.

11 Q. And do you recall you told me at your deposition that the  
12 opinions set forth in your expert report were developed from  
13 June through August of 2014? Do you recall that?

14 A. I believe so.

15 Q. Now, if you could take a look at DTX-1168 previously  
16 marked at your deposition as Deposition Exhibit 4.

17 MR. O'MALLEY: We're not going to go -- we probably  
18 don't need to go into the substance of this, your Honor, but  
19 it's in the rack if you need it. It is just a couple  
20 questions. Mostly regarding dates and overall content.

21 BY MR. O'MALLEY:

22 Q. Do you understand what this document is?

23 THE COURT: He can read the title. I don't think you  
24 can ask him if he understands what it is.

25 BY MR. O'MALLEY:

—Fruehauf - Cross—

1 Q. Well, let me read the title into the record. It's "Teva  
2 Pharmaceutical U.S.A., Inc. and Teva Pharmaceutical  
3 Industries, Limited, Invalidity Contentions Pursuant to  
4 L.Pat.R.3.6(c)."

5 Do you see that?

6 A. Yes.

7 MR. WONG: Objection. Counsel asked the witness the  
8 same question at his deposition, and there's no foundation.

9 THE COURT: I'll listen.

10 BY MR. O'MALLEY:

11 Q. And do you see that this document is dated, and we can go  
12 to -- should be .0128 dated March 17, 2014?

13 A. Uh-huh.

14 Q. So, this document was completed prior to the time you  
15 developed your opinions in this case, correct?

16 A. I believe so. I'm not really sure about all the dates.

17 Q. Okay. Well, you told me that your opinions were from  
18 June to August, correct? Developed from June to August?

19 A. It's an approximate -- it's an approximate estimation. I  
20 don't know the exact dates.

21 Q. But that's what you told me at your sworn deposition.

22 A. Yes.

23 Q. And you see this is dated a couple months before that,  
24 correct?

25 A. Evidently, yes.

—Fruehauf - Cross—

1 Q. Okay. So, if the dates you told me were accurate at your  
2 deposition, then this document was completed prior to the time  
3 you developed your opinions in this case, correct?

4 A. Evidently.

5 Q. And do you recall we looked at DTX-1168.0093 under  
6 heading C?

7 A. During my deposition?

8 Q. During your deposition. We'll get there in a moment.

9 And if you recall, this summarized Teva's opinions  
10 regarding lack of written description. Do you recall  
11 generally us --

12 A. Yes.

13 Q. -- discussing that?

14 A. Yes.

15 Q. And at your deposition, you agreed that Teva's invalidity  
16 contentions with respect to lack of written description were  
17 roughly the same opinion that you provided in your summary  
18 opinions in your August 15, 2014 report.

19 Do you recall that?

20 A. Yes.

21 Q. Now, you were not involved in reviewing or preparing any  
22 drafts of Teva's invalidity contentions, correct?

23 A. Not that I know of.

24 Q. Okay. Now, I'd like to discuss your opinion that you  
25 provided at the end of your testimony this morning regarding

—Fruehauf - Cross—

1 the conclusion that the '219 claims are invalid for lacking  
2 adequate written description, okay?

3 A. Uh-huh.

4 THE COURT: Mr. O'Malley, I do not hear that in Dr.  
5 Fruehauf's testimony here, and expert reports are not  
6 evidentiary. They're not admitted as exhibits.

7 MR. O'MALLEY: Your Honor, about five, six questions  
8 back, he admitted that that was the gravamen of those opinions  
9 that he offered at the end of the day.

10 THE COURT: He said he was asked questions about  
11 those, about that topic.

12 You can elicit an opinion from him if you want, but I'm  
13 sorry, maybe I misheard.

14 MR. WONG: That's correct, your Honor. I never asked  
15 the witness his overall opinion on the written description  
16 defense.

17 MR. O'MALLEY: Okay. We will assume that opinion is  
18 not in evidence.

19 THE COURT: Is that right, Mr. Wong? Not from Dr.  
20 Fruehauf.

21 MR. WONG: To be clear, I asked him about facts  
22 related to his review of the patent specification. I did not  
23 elicit his overall opinion on the written description defense.

24 THE COURT: That's right. You didn't.

25 BY MR. O'MALLEY:

—Fruehauf - Cross—

1 Q. Okay. Now, let's take a look at the '219 patent, and  
2 let's look at Claim 1 and look at lines -- let's look at the  
3 preamble, and let's start with 4 in the preamble "for  
4 intravenous administration to a human to reduce the likelihood  
5 of cancer chemotherapy-induced nausea and vomiting."

6 Do you see that?

7 A. Yes, sir.

8 Q. Now, first of all, in the U.S. in order to treat a human  
9 with a pharmaceutical formulation to reduce the likelihood of  
10 CINV, that pharmaceutical single-use unit-dose formulation has  
11 to be approved by the FDA, correct?

12 A. You know, there are natural products that are used for  
13 reducing nausea in patients, like ginger; but if you're  
14 talking about a drug that's for the purpose that's on a  
15 package insert, then, yes, it requires FDA approval.

16 Q. Now --

17 THE COURT: And you couldn't get a formulation of  
18 ginger and inject it.

19 THE WITNESS: People do things like that.

20 THE COURT: Okay. Never mind.

21 BY MR. O'MALLEY:

22 Q. Now, in your opening expert report -- well, let me strike  
23 that.

24 Today when you were asked about the subject matter of  
25 the '219 patent, you said it relates to a formulation and it

—Fruehauf - Cross—

1 relates to stability.

2 Do you recall that testimony?

3 A. Yes.

4 Q. And you didn't state that it relates in any manner to  
5 the likely -- to the intravenous administration to a human to  
6 reduce the likelihood of cancer chemotherapy-induced nausea  
7 and vomiting.

8 Do you recall you didn't discuss that as part of the  
9 subject matter of this patent? Do you recall?

10 A. No, I did. I said that I believe the patent is based on  
11 a formulation for stability, but there is a component within  
12 the claim, which was determined to be a limitation, where my  
13 being a person in the skill of the clinical sciences impinges  
14 on that component of the first section, which is when you  
15 start to give things to humans -- now we're not talking about  
16 a formulation. Now we're talking about a clinical use and a  
17 claim about reducing nausea and vomiting in people, so --  
18 that's related to chemotherapy.

19 Q. Now, I just want to make sure I understand. Is your  
20 testimony now that the preamble is part of the subject matter  
21 of the '219 patent?

22 A. I am not an attorney to make decisions about that.

23 Q. So, you have no --

24 A. I'm not a patent attorney.

25 Q. You have no opinion on that now.



—Fruehauf - Cross—

1 A. I was just -- no. I was asked to give an opinion as a  
2 person of skill in the art of the clinical sciences, which is  
3 different than a POSA, who's a formulator, to address that  
4 element of the claim which was determined to be a limitation,  
5 that it's used for treating people with chemotherapy-induced  
6 nausea and vomiting. So, they have asked me to come and talk  
7 about that part of the claim.

8 Q. Now, I'm talking about the question you were asked this  
9 morning to the effect of what is the subject matter of the  
10 '219 patent.

11 Do you recall that question?

12 A. Yes.

13 Q. And do you recall your answer was limited to the  
14 formulation and to stability?

15 A. I believe --

16 Q. Do you recall that?

17 A. That's my opinion.

18 Q. That's your opinion.

19 So, this preamble then, therefore, logically is not  
20 part of the subject matter of the patent.

21 MR. WONG: Objection.

22 THE COURT: Sustained. He can't be drawn into that  
23 dispute. We've resolved it as a legal matter.

24 BY MR. O'MALLEY:

25 Q. Now, in your opening expert report, you state -- you

—Fruehauf - Cross—

1 stated that nothing in the '219 disclosure relates to reducing  
2 CINV specifically.

3 Do you recall that?

4 A. This morning?

5 Q. In your expert report.

6 A. In my expert report?

7 Q. Yeah.

8 A. I was referring to the fact that there's no clinical data  
9 to support the claim in the body of the patent.

10 Q. Beyond clinical data, you know or you realize that  
11 there's a number of excerpts of the disclosure that discuss  
12 treatment of CINV specifically without data; do you realize  
13 that?

14 A. Yes.

15 Q. Okay. Now, in this afternoon you offered opinions that  
16 discussed the fact that there was no data in the patent  
17 specification.

18 Do you recall that?

19 A. I believe that Mr. Wong asked me if I had seen any of the  
20 Phase III clinical trial data anywhere in the patent, and I  
21 answered no.

22 Q. Okay. Now, you're aware that this hypothetical person of  
23 ordinary skill in the art has all the relevant publicly  
24 available prior art before him or her, correct?

25 A. I'm not sure what that means.

—Fruehauf - Cross—

1 Q. You're not -- you don't have any opinion on that one way  
2 or the other?

3 A. Maybe if you ask the question a different way.

4 Q. Well --

5 THE COURT: It depends for what purpose, I would say.

6 BY MR. O'MALLEY:

7 Q. Are you aware that the hypothetical person of ordinary  
8 skill in the art for the purpose of interpreting the patent  
9 and the prior art has all the relevant --

10 THE COURT: And the prior art?

11 BY MR. O'MALLEY:

12 Q. -- and the prior art has all the relevantly publicly  
13 available prior art before him or her?

14 A. This is a question of the public availability?

15 Q. That was part of the question, yes. Are you aware of  
16 that?

17 MR. WONG: Objection, Your Honor, to the extent it  
18 goes to a legal issue or a legal conclusion.

19 THE COURT: He can explore a little bit.

20 MR. O'MALLEY: Do you understand that?

21 THE COURT: Well, is your question directed to how  
22 would a person of ordinary skill in the art, looking at a  
23 patent in which they are a person of ordinary skill in the  
24 art, read that patent? How would that person understand that  
25 patent?

—Fruehauf - Cross—

1 MR. O'MALLEY: Yeah. It is really more general than  
2 that with respect to almost any doctrine in patent law; but  
3 the point is when Dr. Fruehauf and I discussed this at his  
4 deposition, he did have a clear understanding of this  
5 doctrine.

6 THE COURT: Are we talking about claim  
7 interpretation, or are we talking about obviousness, or are we  
8 talking about on-sale bar?

9 MR. O'MALLEY: I believe that with respect to all of  
10 those doctrines as a matter of patent law, the POSA is  
11 presumed to have the prior art in front of him and her and  
12 uses that body of knowledge whether it's to interpret what a  
13 claim limitation means, whether to judge whether a claim is  
14 obviousness, et cetera.

15 THE COURT: Well, sir, at least -- and this is beside  
16 the point of Dr. Fruehauf's knowledge, so give us a second.

17 THE WITNESS: Yes, ma'am.

18 THE COURT: At least we know that the POSA looks for  
19 certain questions at a patent. He looks at the patent as of  
20 the date it was applied for.

21 MR. O'MALLEY: Very true.

22 THE COURT: You know, and then for this on-sale bar  
23 business, he needs to look at what has been called a critical  
24 date, which is a year before.

25 And I'm not going to allow Dr. Fruehauf to be

—Fruehauf - Cross—

1 instructed on whether publicly available information for  
2 purposes of the on-sale bar is all a POSA is assumed to know.  
3 So, if you would like to continue to inquire, please feel free  
4 to do so, but make your question clear to him.

5 MR. O'MALLEY: Sure.

6 BY MR. O'MALLEY:

7 Q. Now, let me build on the judge's observation.

8 With respect to the notion -- you've reviewed -- let me  
9 back up -- Dr. Saab's and Dr. Peck's report.

10 A. Yes.

11 Q. And you have reviewed their opinions relating to whether  
12 a person of ordinary skill reviewing the patent description  
13 and disclosure as of the date the patent was filed would  
14 believe the inventors to be in possession of the invention.

15 Do you recall that?

16 A. Yes.

17 Q. And, so, you're aware that the focus on that analysis is  
18 on the date the patent application is filed, correct?

19 A. Yes.

20 Q. Okay. Now, with respect to this -- you've also seen  
21 testimony relating to whether the patent-in-suit was on sale;  
22 is that correct?

23 A. Yes.

24 THE COURT: Opinions, you mean.

25 MR. O'MALLEY: Opinions.

—Fruehauf - Cross—

1 BY MR. O'MALLEY:

2 Q. And you're aware that focus for that analysis is one year  
3 prior to the patent application date, correct?

4 A. I believe I heard testimony to that effect on Tuesday.

5 Q. Okay. Now, in terms of our case, you're aware that some  
6 significant information enters the public domain regarding the  
7 status of Helsinn's development efforts in that one-year  
8 period between the critical date and the filing dates of the  
9 patents, correct?

10 A. I'm not sure what information you're speaking of that  
11 reached the public domain.

12 Q. Sure. Let's turn to PTX-0297.

13 And, again, it's in your -- it's in your notebook. You  
14 can look at as much as you like. And you've seen that  
15 document before?

16 A. I don't recall.

17 Q. Why don't we turn to the conclusion section at the bottom  
18 of the chart.

19 Do you recall us reviewing this publication at your  
20 deposition?

21 A. I don't recall, but I'll accept your assertion.

22 Q. Okay. And you see the date of this publication if we go  
23 back to the first page, June 23 to 26, 2002.

24 Do you see that?

25 A. Yes, yes.

—Fruehauf - Cross—

1 THE COURT: Is this a paper presented at that  
2 meeting, conference?

3 MR. O'MALLEY: Well, perhaps I should ask the  
4 question.

5 BY MR. O'MALLEY:

6 Q. You understand this to be an abstract?

7 A. It says "oral presentation."

8 Q. Okay. And what form of publication is this, to your  
9 understanding?

10 A. I guess the -- there may be a journal of the  
11 Multi-National Association of Supportive Care In Cancer.

12 Q. Okay.

13 A. Usually they will publish a proceedings for their  
14 journal, which would include abstracts from the national  
15 meeting. And while the oral presentation is not included in  
16 the publication, the abstract is included in the publication.

17 Q. And you understand that an abstract like this would be  
18 publicly available in this case prior to the filing date of  
19 the '219 patent?

20 A. Yes, sir.

21 Q. Okay. And then if we look at the conclusions -- well,  
22 first of all, if we blow up the box above the conclusions.

23 Now, you recall or perhaps you now note that this MASCC  
24 abstract reports some Phase III clinical data for palonosetron  
25 with respect to CINV?

—Fruehauf - Cross—

1 A. These data look to me to be from 99-04.

2 Q. Okay. And you understand that to be Phase III clinical  
3 data for palonosetron with respect to treatment of CINV.

4 A. Yes.

5 Q. And you see that there is some treatment rate reported  
6 there?

7 A. Yes.

8 Q. And for the .25, the acute response is 63 percent.

9 Do you see that?

10 A. The -- that would be the complete response in the acute  
11 phase.

12 Q. Yes.

13 A. Of 63 percent control.

14 Q. Right. And there is data for complete response in the  
15 delayed phase, 24 to 120 hours.

16 Do you see that?

17 A. Yes, sir.

18 Q. And for .25 milligrams, there's a response rate report of  
19 54 percent?

20 A. Yes.

21 Q. And do you see that --

22 THE COURT: The comparator is different in that 04  
23 Phase III study, isn't it?

24 THE WITNESS: It was dolasetron here, and it was  
25 dolasetron was --



—Fruehauf - Cross—

1 THE COURT: At 100 milligrams.

2 THE WITNESS: At 100 milligrams.

3 THE COURT: Okay. Fine.

4 THE WITNESS: So it's a setron that was less potent  
5 than ondansetron.

6 BY MR. O'MALLEY:

7 Q. Now, if we go to the conclusion, it states, "Palonosetron  
8 has demonstrated significant activity in preventing both acute  
9 and delayed emesis with a single I.V. dose. In patients  
10 receiving moderately emetogenic chemotherapy, palonosetron was  
11 safe and well tolerated."

12 Do you see that?

13 A. Yes, I do.

14 Q. And you agree that the data supports that conclusion,  
15 correct?

16 A. Yes.

17 Q. Now, in your opening report, you stated -- and if you  
18 don't recall this, we'll put it in front of you -- "Phase II  
19 trials are designed to assess and establish an indication of  
20 clinical efficacy of the drug compound for treating particular  
21 disease conditions or symptoms," correct?

22 A. I'm not sure if those are the exact words, but --

23 Q. Well, why don't we pull up DTX-1179-0010, Paragraph 23.  
24 And we've highlighted the words, and let me just read that  
25 into the record, and I'll finish the sentence for

—Fruehauf - Cross—

1 completeness: "Phase II trials are designed to assess and  
2 establish an indication of clinical efficacy of the drug  
3 compound for treating particular disease conditions or  
4 symptoms, and includes finding the minimum effective dose of  
5 the drug."

6 Do you see that?

7 A. Yes, sir.

8 Q. And you were in the courtroom when Dr. Calderari  
9 testified?

10 A. Yes.

11 Q. And you heard that he called it -- he referred to it as a  
12 signal of efficacy.

13 Do you recall that?

14 A. Yes. That's a pharma -- pharmaceutical company jargon.

15 Q. Okay. And indication of clinical efficacy, does that  
16 mean something different than Dr. Calderari's signal? I  
17 believe in your direct testimony, you likened the two terms.

18 A. I agree.

19 Q. Okay. Now, you provided some opinions regarding 2330,  
20 the Helsinn's -- well, Syntex's Phase II study, correct?

21 A. Yes.

22 Q. And Study 2330 reported data as you noted for a  
23 3-microgram-per-kilogram dose, correct?

24 A. Yes.

25 Q. And that corresponds to roughly a .21-milligram total

—Fruehauf - Cross—

1 dose; is that correct?

2 A. Yes. I think that we were sort of rounding it to the  
3 .25.

4 Q. Fine. I'm making no distinction.

5 The study also reported data on other doses, correct?

6 A. Yes, it did.

7 Q. There was the .3- to 1-microgram-per-kilogram dose,  
8 correct?

9 A. Well, those were separate doses, but those doses were  
10 combined into one category.

11 Q. Right.

12 A. So, there's that one category of the lower doses combined  
13 together.

14 Q. And those lower doses combined together were considered  
15 the control in the study.

16 Do you understand that?

17 A. I believe that was the intent.

18 Q. Okay. And then there was a number of other doses,  
19 1 microgram per kilogram, correct?

20 A. Point -- it was .3 to 1 was the low dose.

21 Q. I'm sorry. I didn't mean this to be a memory test. Why  
22 don't we get it up there. DTX-0227-0015.

23 And let's highlight the summary and conclusions and  
24 down through the chart and footnote.

25 So, the other doses studied besides what was intended

—Fruehauf - Cross—

1 to be the control, as you put it, were the 3 microgram per  
2 kilogram, correct?

3 A. Yes.

4 Q. The 10 microgram per kilogram?

5 A. Yes.

6 Q. The 30 microgram per kilogram, and the 90 microgram per  
7 kilogram?

8 A. Yes, sir.

9 Q. Now, if you look at the summary and conclusions, it  
10 concludes that "All four doses were approximately equally  
11 effective as compared with the combined results from a cohort  
12 of .3 and 1 microgram per kilogram."

13 Do you see that?

14 A. Yes.

15 Q. And that phrase "cohort" is -- refers to what you mean  
16 they combine the data from doses in that range?

17 A. Yes, sir.

18 Q. Okay. And then it has the table.

19 Now, underneath the table, there is an indication of an  
20 asterisk and with respect to statistically significant  
21 differences p less than .05 versus lowest dose group.

22 Do you see that?

23 A. Yes, I do.

24 Q. And you provided a brief explanation of what this -- what  
25 do we call the p-value in statistics, again?

—Fruehauf - Cross—

1 A. The probability that an event could occur by chance  
2 alone.

3 Q. Right. And this -- this designation under the chart that  
4 regarded statistically significant differences is only those  
5 differences that had a P less than .05. That's rather  
6 standard in the pharmaceutical industry. You know that?

7 A. Yes, it's an arbitrary choice.

8 Q. But it's standard, correct?

9 A. It -- it is a standard.

10 Q. Yes.

11 Now, with respect to the results for complete control  
12 after 23 -- 24 hours, rather, you see there's a value of 24  
13 for the cohort of .3 to 1?

14 Do you see that?

15 A. Yes.

16 Q. And do you see the value for 3 microgram per kilogram is  
17 46?

18 A. Yes.

19 Q. But you recognize that there's no asterisk next to the  
20 46?

21 A. Correct.

22 Q. And according to the authors of this study, that means  
23 there was no statistically significant difference between that  
24 value for complete control at 24 hours and the value for the  
25 cohort, correct?

—Fruehauf - Cross—

1 A. That is correct from a statistical perspective.

2 Q. Okay. Now, in fact --

3 THE COURT: Is there an asterisk on some of those  
4 hour figures down on the bottom row? But not otherwise.

5 THE WITNESS: Yes, that's right. 22.7 has the  
6 asterisk for the time to failure, so that was statistically  
7 significantly different for the .25 compared to the .3 to 1.

8 BY MR. O'MALLEY:

9 Q. Now, in reviewing these clinical trials, you're familiar  
10 with the notion of a primary endpoint.

11 A. Yes, sir.

12 Q. And can you explain to the judge what primary endpoint  
13 means?

14 A. The primary endpoint would be the endpoint around which  
15 you design your trial.

16 Q. And in this case and in the case of these other clinical  
17 trials you've testified about today, the primary endpoint is  
18 percent complete control, correct?

19 A. Yes.

20 Q. Now, with respect to that primary endpoint, the only  
21 value that showed statistically significant difference  
22 compared to the lowest cohort was the value at 30 microgram  
23 per kilogram, correct?

24 A. Yes.

25 Q. And that's roughly a 2.1-milligram dose roughly; do you

—Fruehauf - Cross—

1 agree with that?

2 A. Yes.

3 Q. Now, you're aware that in general the FDA will not allow  
4 you to claim an indication if you do not show statistical  
5 significance for an outcome for a primary endpoint in the  
6 study. You're aware of that, correct?

7 A. Yes.

8 THE COURT: Could I just interpose one question,  
9 please?

10 MR. O'MALLEY: Certainly.

11 THE COURT: Just looking at our column for the  
12 3-microgram dosage, and it says 46 percent --

13 THE WITNESS: Yes, ma'am.

14 THE COURT: -- complete control in the first  
15 24 hours. This is 46 percent of the people tested reported  
16 complete control; is that what it's telling us?

17 THE WITNESS: 46 percent of the people who got the  
18 drug --

19 THE COURT: Right.

20 THE WITNESS: -- had complete control compared to  
21 24 percent of the patients who got only .3 to 1, and I had  
22 testified earlier that you can imagine there's people that  
23 would get nothing. There's zero.

24 THE COURT: Right.

25 THE WITNESS: But here we're comparing 3 to .3 to 1,

—Fruehauf - Cross—

1 where there's some benefit from the .3 to 1, and -- but they  
2 combine that data just to have some comparator, but it may  
3 come out later what was actually asked for.

4 THE COURT: No, the direction of my question was just  
5 that that number, 46, is percentage of patients receiving the  
6 particular drug at that dosage who exhibited or reported  
7 complete control --

8 THE WITNESS: Yes, ma'am.

9 THE COURT: -- of their symptoms.

10 THE WITNESS: Yes, ma'am.

11 THE COURT: So, no nausea.

12 THE WITNESS: No nausea and no need for rescue  
13 medication.

14 THE COURT: Okay. If they were, like, you know,  
15 better, but not greater on the nausea scale, they didn't make  
16 it into the 46 percent, right?

17 THE WITNESS: Correct. They could have had a  
18 benefit, but it wouldn't have been to the degree that was  
19 required for this analysis.

20 THE COURT: Okay.

21 BY MR. O'MALLEY:

22 Q. Now, you're aware, Dr. Fruehauf, that the FDA concluded  
23 that study 2330 did not establish efficacy, correct?

24 A. My opinion on that question --

25 Q. I didn't ask your opinion on that question.



—Fruehauf - Cross—

1 A. But it has to do with the context of what their decision  
2 was.

3 Q. Are you aware that the FDA concluded that; yes or no?

4 A. Eventually, they did conclude that it was.

5 Q. Eventually they --

6 A. That's why they allowed it to go to the Phase II -- Phase  
7 III.

8 Q. Dr. Fruehauf, let me ask my question again. Are you  
9 aware that the FDA concluded that the Study 2330 did not  
10 establish efficacy?

11 A. There were various communications with the FDA about  
12 whether the .25 dose was correct as being the minimally  
13 effective dose.

14 Q. Now, let me pull up the transcript at Page 165:17 to  
15 165:5.

16 "QUESTION: Now, are you aware" --

17 THE COURT: What transcript are you reading from?

18 MR. O'MALLEY: Dr. Fruehauf's transcript.

19 THE COURT: Deposition?

20 MR. O'MALLEY: Deposition transcript, thank you.

21 BY MR. O'MALLEY:

22 Q. And I passed up a copy of that.

23 "QUESTION: Are you aware that the FDA concluded in  
24 reviewing this data that it could not be used as evidence of  
25 efficacy because of a lack of dose response?

—Fruehauf - Cross—

1           "ANSWER: You know, I've heard that -- I've seen  
2 that. And I think that, you know, I did work closely with the  
3 FDA when I was at NCI as a fellow and CBER and those people.  
4 I even imagined at one time that I might even work in the FDA.  
5 And, you know, those are human beings, just like the patent  
6 reviewer people are human beings, and they can make mistakes."

7           Did I read that correctly?

8           MR. WONG: Objection, Your Honor. That's not  
9 impeachment.

10           THE COURT: He can ask whether this has been read  
11 correctly, Mr. Wong.

12 BY MR. O'MALLEY:

13 Q. Did I read that correctly?

14 A. That's read correct.

15           MR. O'MALLEY: Let's pull up PTX-0261, Page 5, and  
16 let's go down to --

17           THE COURT: Now, what is this?

18           MR. O'MALLEY: Let's go to the cover page of this.

19 BY MR. O'MALLEY:

20 Q. And do you recall that Dr. Calderari presented some  
21 testimony regarding this document during his testimony?

22 A. Yes, sir.

23 Q. And do you recall that this was described by him as an  
24 end of Phase II meeting minutes?

25 A. Yes, sir.

—Fruehauf - Cross—

1 Q. And that the meeting minutes were prepared by the FDA?

2 A. Yes, sir.

3 Q. And the date of this is March 10, 1999.

4 Do you see that?

5 A. Yes, sir.

6 Q. And Dr. Calderari testified that he attended that  
7 meeting, correct?

8 A. Yes, sir.

9 Q. Now, if you go down to Page 0005 in Question 6, and you  
10 understand that the format of this document is that the  
11 pharmaceutical company poses certain questions at the meeting  
12 in the minutes with the highlighted bullet points are meant to  
13 summarize the FDA's response to those questions?

14 A. Yes, sir.

15 Q. Okay. And in Question 6 Helsinn asked, "Is 2330  
16 sufficient to support the label claim 'including high-dose  
17 Cisplatin' should a historical control analysis be conducted?"

18 Do you see that?

19 A. Yes, sir.

20 Q. And I'll skip down to the bullet: "Due to the lack of a  
21 dose response in this study, these data are inadequate to  
22 serve as pivotal efficacy support (although they may be useful  
23 as supportive data)."

24 Do you see that?

25 A. Yes, sir.

—Fruehauf - Cross—

1 Q. Now, when we discussed this at your deposition, do you  
2 believe -- do you recall telling me that you believed the FDA  
3 was wrong?

4 A. Well --

5 Q. Yes or no; do you recall that?

6 A. Yes.

7 Q. Okay.

8 A. But that was in a different context.

9 Q. I see.

10 Now, are you aware that Helsinn was asked to reanalyze  
11 Study 2330 by the FDA?

12 A. Yes.

13 Q. Now, in discussing why you thought the FDA was wrong in  
14 specific to this conclusion, you testified that "I would think  
15 if they were pharmacologists, they would have come to a  
16 different conclusion or they didn't look at all the data  
17 correctly."

18 Do you recall providing that testimony?

19 A. Yes.

20 Q. And, again, you've never been personally involved in the  
21 selection of a specific dosage of a drug in a treatment that  
22 was eventually approved by the FDA, correct?

23 A. Yes.

24 Q. Now, let's look at -- you cited to the August Consulting  
25 letter, DTX-0293. Can we pull that up?

—Fruehauf - Cross—

1           Do you recall providing testimony about that document  
2 in your --

3 A. Yes, sir.

4 Q. -- direct testimony?

5 A. Yes, sir.

6 Q. Do you need -- okay. You got some water.

7           Turning to Page 30 in the document, the last line of  
8 the third paragraph reads -- if we can highlight that, Roy --  
9 "Results achieved in Phase II CINV studies suggest that  
10 palonosetron is safe and effective in preventing nausea and  
11 vomiting following emetogenic chemotherapy, especially during  
12 the 24 hours after administration."

13           Now, the word "suggest" as you interpret it from your  
14 POSA in the clinical sciences standpoint, is that the same  
15 thing, does that have the same meaning as "signal" or  
16 "indication" as we discussed before, suggestion?

17 A. It has the meaning of probability from the standpoint of  
18 that it's likely to reduce the risk, and likely to reduce the  
19 risk is not a statistical assertion, so likely to reduce the  
20 risk/suggest go together, likely and suggest.

21 Q. Now, looking further down to the last line of the page,  
22 it states that "This study is designed to support the  
23 hypotheses that palonosetron is not inferior to currently  
24 available 5-HT<sub>3</sub> receptor antagonists and is effective in  
25 preventing nausea and vomiting following moderately emetogenic

—Fruehauf - Cross—

1 chemotherapy."

2 The study they're referring to, again, is Study 2330.

3 Do you understand that?

4 A. They've referred to it in the past tense already. It  
5 said, "Given the high affinity and efficacy results in both  
6 end walls in Phase II" --

7 Q. Yeah, and, by the way, why don't I interrupt you because  
8 I misspoke. This is referring to study, as you testified,  
9 99-03, correct?

10 A. Right. It's not for the Phase II study.

11 Q. Yeah. And, so, you agree that this is an accurate  
12 description of the hypotheses that Study 99-03 was designed to  
13 test?

14 A. Yes, 99-03 was designed to test a noninferiority  
15 endpoint.

16 Q. And you understand in order to get a MEC indication from  
17 the FDA, they needed an additional study, 99-04 in addition to  
18 this noninferiority study, 99-03, correct?

19 A. Um, I don't know what the FDA told them as to what would  
20 be required for approval.

21 Q. You're not aware that that was an agreed-upon requirement  
22 between Helsinn and the FDA?

23 A. No. I know that they went and they had their meeting and  
24 they discussed all three trials, three studies.

25 Q. But are you aware then in order to get an indication for

—Fruehauf - Cross—

1 MEC, they had to have a successful showing not only in 99-03,  
2 the noninferiority study, but, also, in 99-04?

3 A. You know, as to what would happen after the results of  
4 those trials are in and when they filed or for an NDA, it's  
5 hard to say; but I think the pre-IND meeting that they had,  
6 that the FDA is telling them, gee, if you do a good job on  
7 these studies, you have a high likelihood of getting approval.

8 Q. So, you don't understand that prior to Phase III, there  
9 was an agreement at that time between Helsinn and the FDA that  
10 they would need to show a successful outcome, not only  
11 in 99-03 for MEC, but, also, 99-04 for MEC; you don't  
12 understand that?

13 A. No, I understand that, you know, they tried to get, you  
14 know -- they tried use the Phase II study as the pivotal  
15 study. That was the prior discussion we had.

16 They didn't allow them to use it as the pivotal study  
17 for purposes of approval, so they said if you want approval,  
18 you need to do pivotal studies, and they told them to do --

19 THE COURT: Before Phase III?

20 THE WITNESS: They tried to -- the prior discussion  
21 was related to trying to use the Phase II study as the  
22 labeling study.

23 THE COURT: Don't you always have to do Phase III  
24 studies?

25 THE WITNESS: Not always. But because they did this

—Fruehauf - Cross—

1 prospective, randomized, double-blinded Phase II study, but  
2 they were told no, you didn't get this right, you didn't get  
3 that right, you need to go forward and do Phase III studies.

4 BY MR. O'MALLEY:

5 Q. My question is more specific, and if you can't answer it,  
6 just please tell me and I'll move on.

7 Did you understand that prior to Phase III that Helsinn  
8 understood, and the FDA had so told them, that in order to get  
9 an indication for MEC, they had to have a successful outcome  
10 out of both 99-03 and 99-04?

11 A. For moderately emetogenic chemotherapy --

12 Q. Yes.

13 A. For moderately emetogenic chemotherapy --

14 Q. Okay.

15 A. -- because that was the key, was the indication was  
16 moderately emetogenic chemotherapy.

17 Q. Correct, and to get an indication for HEC, highly  
18 emetogenic chemotherapy, they needed, one, to reanalyze the  
19 2330 Study and get a successful outcome in 99-05.

20 Do you understand that?

21 A. Yes. They were going to allow them to use the Phase II  
22 study as supportive data, so they really only needed one Phase  
23 III trial for highly emetogenic chemotherapy and then based on  
24 the Phase II study and the Phase III, they would approve it  
25 for that indication.



—Fruehauf - Cross—

1 THE COURT: But they did have to reanalyze the Phase  
2 II HEC data --

3 THE WITNESS: And that's what --

4 THE COURT: -- is that right?

5 THE WITNESS: Yes, because I was, you know saying  
6 earlier, you can imagine if you had no treatment. So they  
7 went back and they put in a sort of like if it was a placebo  
8 category of historical controls, and then they reran their  
9 statistical analysis, and now it was significant.

10 BY MR. O'MALLEY:

11 Q. But it wasn't before in the FDA's eyes, in any event?

12 A. No. It wasn't adequate for labeling at that time.

13 That's really the distinction. In other words, the context  
14 was they didn't feel it was adequate for labeling at that  
15 time.

16 Q. Now, let's turn to the Formulation Book DTX-0254.

17 And you've reviewed this book before?

18 A. I don't remember seeing the Formulations Book.

19 Q. I'm sorry?

20 A. I don't remember seeing the Formulation Book. I knew it  
21 was discussed at the -- I know it was previously discussed. I  
22 can't remember looking at it.

23 Q. Okay. Are you aware, and we can go through it if we need  
24 to, that as a result of its analysis or analyses of the Phase  
25 II study, 2330, that Roche/Syntex recommended a dose for Phase

—Fruehauf - Cross—

1 III clinical trials for CINV of 1 milligram?

2 A. This is May 1995?

3 Q. This publication is, yeah.

4 A. So, you're referring to this publication?

5 Q. My question is more general.

6 Are you aware that Roche/Syntex made that  
7 recommendation based on its analyses of Study 2330?

8 A. At what time?

9 Q. At any time.

10 A. I don't remember seeing that --

11 Q. So you're not aware --

12 A. -- in the material I read.

13 Q. You're not aware of that?

14 A. I'm not aware of that.

15 Q. Why are you focusing on the time frame in this question?

16 A. I was trying to understand what the Formulation Book is.  
17 I don't know this and how that would relate to clinical  
18 trials' outcomes.

19 Q. Are you aware of when 2330 was finalized?

20 A. I thought it was June of 1995.

21 MR. O'MALLEY: Okay. And in that, why don't -- can  
22 we pull out 2330. And find the signature page. Likely around  
23 the last page, Roy.

24 BY MR. O'MALLEY:

25 Q. Now, while he's looking for that, with respect to the

—Fruehauf - Cross—

1 date that the final report is signed, that's a date that you  
2 have in mind? Whether it's accurate or not, you're thinking  
3 of the date the final report was signed?

4 A. Yeah, I mean, I'm thinking about it would be difficult to  
5 reach a conclusion without knowing the 2330 data about what  
6 dose should go forward, and you need to go through a whole lot  
7 of different processes, so July 1995.

8 Q. Do you recognize this to be the final report for 2330?

9 A. Yes. And the report is July 1995.

10 Q. And let's go to the last page.

11 And you see it was signed even after that in September  
12 of 1995?

13 A. Yes.

14 Q. Now, are you aware the Formulation Book discusses the  
15 results of Study 2330?

16 A. No.

17 Q. No. But you are aware that results are available, that  
18 seemed to be a theme of your testimony this morning, before  
19 the final report on any given study is both prepared and  
20 signed, correct?

21 A. Now this Phase II study would be much more difficult to  
22 try and do an analysis on blinded data, if that's what you're  
23 alluding to.

24 Q. No, I'm just saying before the final study report is  
25 executed and signed, often results are available, preliminary

—Fruehauf - Cross—

1 may they be, correct?

2 A. I don't know when the, you know, data analysis were done.  
3 I just -- what I'm saying is, to me, the company prepared this  
4 report and finally signed it in September of 1995, and you're  
5 showing me a book from May. So I don't know what the  
6 connection is between who was writing these different things  
7 and what they were referring to and thinking about when they  
8 wrote them.

9 Q. But, in any event, you're not aware that Roche/Syntex  
10 made a recommendation based on its review of Study 2330 that  
11 Phase III trials employ 1 milligram total dose in CINV?

12 A. I'm not aware of that.

13 Q. Okay.

14 A. I'm not aware of that.

15 Q. Let's turn to DTX-1023.

16 Now, in your expert report, you discuss the fact that  
17 you reviewed Dr. Candiotti's expert reports and exhibits. Do  
18 you believe that?

19 A. Candiotti?

20 Q. Candiotti.

21 A. Yes.

22 Q. And do you recall this was one of Dr. Candiotti's  
23 exhibits?

24 A. I don't remember, but I'll say yes, I mean.

25 Q. Okay. Now, this is a letter dated January 7, 1998 from

—Fruehauf - Cross—

1 Kathleen Lee.

2 Do you see that?

3 A. Yes.

4 Q. And you are aware Dr. Lee is listed as one of the  
5 inventors on the face of the patents-in-suit?

6 A. Okay. Yes.

7 Q. And you were here when Dr. Calderari testified that she  
8 was formerly, before this date of this document, affiliated  
9 with Roche Palo Alto, which was formerly Syntex, correct?

10 A. Yes.

11 Q. And you heard that Dr. Lee oversaw Phase II palonosetron  
12 clinical studies while at Syntex?

13 A. Yes.

14 Q. Now, if you turn to the first page of this document and  
15 the first sentence of the third paragraph, it states, "The  
16 RS-25259-197 program was halted by Roche following completion  
17 of clinical Phase II studies."

18 Have you heard testimony about that?

19 A. Yes.

20 Q. Now, are you aware that prior to terminating the  
21 palonosetron project, I know you said you weren't aware of the  
22 specific dose, but are you aware that Roche did, in fact,  
23 determine a dosage of palonosetron to carry forward to the  
24 clinical studies?

25 A. I'm not aware of that.

—Fruehauf - Cross—

1 Q. Could you turn to the second page, the table?

2 And specifically let's turn to 003, and do you see a  
3 product definition?

4 A. Yes.

5 Q. And Table 2 is entitled, "Developmental Assumptions"?

6 A. Yes.

7 Q. And do you see that with respect to the CINE dose that's  
8 defined here, the total dose is 1 milligram?

9 A. Yes.

10 Q. Now, are you aware of any evidence in the documents  
11 you've reviewed whereby Roche/Syntex recommended a dose other  
12 than 1 milligram for Phase III CINV?

13 A. So, I'm understanding, this is Dr. Lee's letter from a  
14 third party now. She doesn't work for Roche or Syntex or --

15 Q. My question has nothing to do with the letter at this  
16 point.

17 A. I'm just trying to understand what we just looked at.

18 Q. My question to you is are you aware of any documents, yes  
19 or no, whereby Roche/Syntex recommends a dose other than  
20 1 milligram for Phase III clinical trials?

21 A. I said I wasn't really aware that they recommended the  
22 1-milligram dose. I don't know about other doses.

23 Q. So, your answer is you're not aware?

24 A. The only thing I'm aware of of what Syntex was saying was  
25 their participation in the meeting with Helsinn, where the

—Fruehauf - Cross—

1 Syntex people that were there cooperated with Helsinn, and  
2 what the conclusions of that joint Syntex/Helsinn meeting  
3 those conclusions were. And we saw from my testimony earlier,  
4 it was .25 and .75.

5 That's the only knowledge I have about the interaction  
6 between Syntex people and Helsinn people on dose selection.

7 Q. Well, to be accurate in that document, it was .25, .75,  
8 and 2 milligrams.

9 A. Correct. I correct myself. There was also a 2-milligram  
10 recommendation, but there was not a 1-milligram  
11 recommendation.

12 Q. Let's look at Roche 7739 to 7742. Have you seen this  
13 document before?

14 A. No, I have not.

15 Q. Now, I'm just going to -- and you understand that Roche  
16 Bioscience was by this time a division of Syntex U.S.A.?

17 A. Gosh, I thought Syntex was a division of Roche.

18 Q. So, you're not aware who Roche Bioscience is?

19 A. I mean, Roche, I believed, acquired Syntex.

20 THE COURT: Maybe Roche Bioscience is actually a sub  
21 under Syntex and Roche --

22 THE WITNESS: Okay. So, I see. So they just  
23 transferred their -- so they have two layers and Syntex is in  
24 between maybe.

25 THE COURT: I don't know.

—Fruehauf - Cross—

1 Counsel, what's the date of this?

2 MR. O'MALLEY: The date of this is 18 October 1995.

3 BY MR. O'MALLEY:

4 Q. Do you see that, sir?

5 A. Yes, I do.

6 Q. And are you aware by this time Roche had decided to  
7 discontinue the palonosetron product?

8 A. I'll accept that.

9 Q. And are you aware that during this period of time, Roche  
10 was looking to out-license palonosetron to a different  
11 pharmaceutical company?

12 A. Okay.

13 Q. And do you see this as a communication to Bristol-Myers  
14 Squibb?

15 Do you see that?

16 A. Yes.

17 Q. And on the second page of this document, there's an  
18 outline of Draft 3 of Draft Phase III Protocol.

19 Do you see that?

20 A. Yes.

21 Q. And under study medications it states, "RS-25259: Based  
22 on the Phase II study results, it is expected that a dose of  
23 1 milligram I.V. RS-25259 will be effective."

24 Do you see that?

25 A. Yes, I do.



—Fruehauf - Cross—

1 Q. And you've not seen this before, I take it?

2 A. No.

3 Q. Now, you referred to a meeting that involves some Syntex  
4 scientists. Was that your 1998 meeting minutes you had in  
5 mind?

6 A. Yes, sir.

7 Q. Why don't we turn to that, PTX-0015.

8 Now, again, you don't have any basis for believing this  
9 document was publicly available, correct?

10 A. I don't know that.

11 Q. You don't know --

12 A. I don't know that it was publicly available or not.

13 Q. Any reason to believe it is?

14 A. No.

15 Q. Do you see in the upper left-hand corner, it says  
16 "confidential"?

17 A. Yes.

18 Q. Now, it appears that these are minutes from a series of  
19 meetings that took place that day?

20 A. Yes.

21 Q. And I believe you were referring to -- well, let me ask  
22 you: In your prior testimony, were you referring to  
23 DTX-15-0008, the minutes of the clinical meeting?

24 A. DTX-0015.

25 Q. 0015-0008. In any event --

—Fruehauf - Cross—

1 A. Yes.

2 Q. -- is this the page you were referring to?

3 A. Correct. Yes, sir.

4 Q. Okay. And I believe you directed our attention this  
5 morning to testimony regarding the CINV proposed doses?

6 A. Yes, sir.

7 Q. And at this point in time among Helsinn internally, the  
8 recommendation was still to keep 2 milligrams as one of the  
9 Phase III doses.

10 Do you see that?

11 A. Yes. Not the 1 milligram, but a different one than they  
12 were, I guess, thinking about earlier. They've switched from  
13 1 to 2 now, but they brought in the .25 and the .75 after  
14 reanalysis of the data with other people from the outside.

15 Q. Sir, do you see that?

16 A. Yes, I see that.

17 Q. Okay. That's all I'm asking you is --

18 A. Yes, sir.

19 Q. -- yes-or-no questions. Your counsel's going to get a  
20 chance to let you pontificate.

21 A. My apologies.

22 Q. Now, that 2.1 -- 2.0-milligram dose, that's equivalent to  
23 30 microgram per kilogram, correct?

24 A. Yes, sir.

25 Q. And you recall when we looked at 2330, the 30 microgram

—Fruehauf - Cross—

1 per kilogram was the only dose that showed statistically  
2 significant difference relative to that cohort, correct?

3 A. For the 24-hour --

4 Q. For the primary endpoint.

5 A. -- complete control. Yes.

6 Q. Yes.

7 Now, do you recall Dr. Calderari's testimony to the  
8 effect that his clinical colleagues were lobbying to test a  
9 higher dose than they eventually tested in Phase III clinical  
10 trials?

11 A. I don't remember that, but I'll accept that.

12 Q. And that he had a concern, based on this balancing,  
13 between efficacy and stability.

14 Do you recall that testimony?

15 A. I do remember that. That went to the -- okay. Yes.

16 Q. And, so, based on his concerns about that balance and how  
17 many doses it was practical for Helsinn to take into Phase  
18 III, they decided that they could not take the 2-milligram  
19 dose into Phase III.

20 Do you recall that generally?

21 A. No, but I'll accept that.

22 Q. Okay. Now, if you turn to the next page of the clinical  
23 meeting minutes, and specifically under CINE dosing, the  
24 minutes from that meeting of the clinical team included a  
25 conclusion that "In a review of the study data, the

—Fruehauf - Cross—

1 3-microgram-per-kilogram dose may not be the most effective."

2 Do you see that?

3 A. Yes, I do.

4 MR. O'MALLEY: I'm not really keeping track of time,  
5 your Honor, so I assume you'll tell me if we get to where you  
6 want to break.

7 THE COURT: You read my mind.

8 MR. O'MALLEY: Okay. Then I'm at a stopping point,  
9 so we can break here.

10 THE COURT: Perfect. Thank you. We'll take a little  
11 recess.

12 (Brief Recess.)

13 THE COURT: Continue.

14 BY MR. O'MALLEY:

15 Q. I would like to turn to DTX-0287-0413. And this is a  
16 declaration you provided testimony about in the morning. Do  
17 you recall that?

18 A. Yes, sir.

19 Q. And for shortness, I'm just going to refer to that  
20 periodically as the Cantoreggi declaration. Is that okay?

21 A. Yes, sir.

22 Q. Now, this is a declaration on -- given by Sergio  
23 Cantoreggi, Enrico Braglia, and Riccardo Braglia. Do you see  
24 that on the first line?

25 A. Yes, I do.

—Fruehauf - Cross—

1 Q. I'm sorry?

2 A. Yes, I do.

3 Q. Okay. And then it states that, in Paragraph 3, "In  
4 particular, we submit this declaration to establish that  
5 Alberto Macciocchi" -- and I'm mispronouncing that and my  
6 client will please forgive me -- "Enrico Braglia and Riccardo  
7 Braglia, had conceived the idea to use palonosetron for the  
8 treatment of acute and delayed-onset CINV, and had conducted  
9 clinical trials in humans to test this idea, at least as early  
10 as October 2, 2001." Do you see that?

11 A. Yes, I do.

12 Q. And although Sergio Cantoreggi is one of the declarants,  
13 there is no assertion in here that he was part of the  
14 conception of the idea to use palonosetron for treatment of  
15 CINV, correct?

16 A. Correct.

17 Q. Now, going back to Paragraph 2, it says, "We submit this  
18 declaration to establish that Alberto Macciocchi, Enrico  
19 Braglia, and Riccardo Braglia had conceived the invention  
20 defined by claim one of this application, and reduced it to  
21 practice, before November 16, 2001, the date that  
22 Dr. Piraccini published abstract Number 5169 in Blood, Volume  
23 98, No. 11 Part 2." Do you see that?

24 A. Yes, sir.

25 Q. What does "reduced to practice" mean?

—Fruehauf - Cross—

1 A. I'm not an attorney. I would not want to take a stab at  
2 that. If there was a clinical thing, to me, it means you're,  
3 you know, doing something for patients, but this is a patent  
4 question.

5 Q. It's a legal term.

6 A. It's a legal term.

7 Q. And you're an American, correct? You live in California.

8 A. Yes, sir.

9 Q. Indeed, you're an inventor on a number of United States  
10 patents, correct?

11 A. Yes, sir.

12 Q. But you're not clear on what the term "reduced to  
13 practice" means. As you put it, it's a legal term.

14 A. It's a legal term.

15 Q. Yeah. Now, you understand that the declarants of this  
16 declaration are Italian speaking?

17 THE COURT: You can assume that.

18 THE WITNESS: I assume that.

19 BY MR. O'MALLEY:

20 Q. Okay. And are you aware that these patents relating to  
21 palonosetron were either their first patents ever or among  
22 their first United States patents ever? Are you aware of  
23 that?

24 A. No.

25 Q. Have you seen any testimony from any of the declarants in

—Fruehauf - Cross—

1 this case?

2 THE COURT: Any of these folks, the four of them?

3 BY MR. O'MALLEY:

4 Q. The declarants, Sergio Cantoreggi, Enrico Braglia or  
5 Riccardo Braglia, have you seen any testimony from them in  
6 this litigation?

7 A. Was it Sergio Cantoreggi here on Tuesday? No. That  
8 was -- that's a different person.

9 THE COURT: Calderari.

10 THE WITNESS: Calderari. I'm confusing the Italian  
11 names. So no, I don't believe I've ever seen them give  
12 testimony.

13 BY MR. O'MALLEY:

14 Q. Okay. So, you have no basis for knowing or speculating  
15 how they interpreted this legal term, "reduced to practice,"  
16 correct?

17 A. No, sir.

18 Q. Now, if you turn to Paragraph 9, it says, "Enrico Braglia  
19 and Riccardo Braglia worked with Dr. Macciocchi as he  
20 developed the clinical protocol for PALO-99-03," and it goes  
21 on from there. As you read that sentence, the "he" clearly  
22 refers to Dr. Macciocchi?

23 A. Yes.

24 Q. Now, nowhere in this declaration does it assert that the  
25 Braglia brothers, and I'll call them that for short, were

—Fruehauf - Cross—

1 personally involved in any aspect of PALO-99-03, other than  
2 working with the person who developed the clinical protocol,  
3 correct?

4 A. Yes. I don't know how to interpret this paragraph in  
5 terms of what intimate knowledge they would have had in the  
6 process.

7 Q. But there is no assertion that they were personally  
8 involved in these clinical studies, correct?

9 A. Just says they worked with him as he developed the  
10 clinical protocol.

11 Q. Now, you've -- are you aware that the Braglia brothers in  
12 the time period when palonosetron was being developed were  
13 co-CEOs of the company? Do you recall Dr. Calderari's  
14 testimony to that effect?

15 A. I remember there was a time I think their father ran the  
16 company and they worked for him and -- but I don't know the  
17 dates of --

18 Q. Okay.

19 A. -- how the family --

20 Q. Fair enough.

21 You've reviewed a number of documents relating to the  
22 clinical studies -- meeting minutes, study reports, et cetera.  
23 Do you recall the Braglia brothers, either one of them,  
24 attending any of these meetings, either with the FDA, with  
25 Syntex, et cetera, to discuss these clinical studies?



—Fruehauf - Cross—

1 A. I don't know.

2 Q. You don't recall that, do you?

3 A. No.

4 Q. Okay. Now, there's no assertion in this declaration that  
5 Dr. Cantoreggi was personally involved in these clinical  
6 studies, correct?

7 THE COURT: You could show him the portions of the  
8 declaration where Dr. Cantoreggi has something attributed to  
9 him.

10 BY MR. O'MALLEY:

11 Q. Yeah, let me see. Let's go back to Page 1.

12 Now, the paragraph with respect to Dr. Cantoreggi's  
13 connection is, I believe, and the only place I see it is  
14 Paragraph 10. It says, "Sergio Cantoreggi has since worked  
15 extensively with Palo and is very familiar with the work  
16 reported in Palo 99-03." Do you see that?

17 A. Yes, I do.

18 Q. And they don't assert the -- whomever drafted this does  
19 not assert that Mr. Cantoreggi was personally involved at the  
20 time with the work reported in PALO-99-03. Do you see that?

21 A. Well, Number 4, they're mentioning.

22 Q. I'm sorry?

23 A. Number 4.

24 Q. Number 4, let me see what you're -- let's pull up Number  
25 4. And what are you -- why are you citing that to me?

—Fruehauf - Cross—

1 A. Well, Sergio Cantoreggi is employed by Helsinn, the  
2 assignee.

3 Q. At the time this declaration is signed?

4 A. Yes. So he was working with the company. That's --  
5 yes, that's what we know.

6 Q. Do you have any basis for knowing that Dr. Cantoreggi was  
7 involved with the clinical trials while they were being  
8 undertaken?

9 A. I don't really know what their management structure was  
10 or how they organized their --

11 Q. You don't know one way or the other?

12 A. No, sir, not one way or the other.

13 Q. When you were listening to Dr. Calderari's testimony, do  
14 you recall him testifying that Dr. Cantoreggi, in the time  
15 period when palonosetron was being developed, worked in the  
16 toxicology lab?

17 A. I don't remember that but I'll accept that as true.

18 Q. Okay. Do you understand that from Helsinn's standpoint  
19 in the relevant time period Dr. Macciocchi was in charge of  
20 the clinical trials?

21 A. It's -- it seems to be that way from this document.

22 Q. And, unfortunately, at the time of this declaration, he  
23 had passed away. Do you understand that?

24 A. No.

25 Q. Okay. It states it but it's not important enough to go

—Fruehauf - Cross—

1 back.

2 A. Okay.

3 Q. Now, you had focused on Paragraph 18 of this declaration.

4 And, as I recall your testimony, you read this to mean that

5 the declarants had seen some indication of success of 99-03

6 before October 2, 2001. Is that fair? Is that an accurate

7 characterization of your testimony?

8 A. Yes, it is.

9 Q. Now, October 2, 2001, is the date the study was

10 completed; is that correct?

11 A. Yes, sir.

12 Q. That's --

13 THE COURT: Last patient out.

14 THE WITNESS: Yes, ma'am.

15 MR. O'MALLEY: Last patient out, correct?

16 THE WITNESS: Yes, sir.

17 BY MR. O'MALLEY:

18 Q. And it's sometime before the data is unblinded, correct?

19 A. Yes, sir.

20 Q. So, for this statement to have been accurate, according

21 to your interpretation, one or more of the declarants would

22 have had to have determined some signal of success prior to

23 the last patient out, correct?

24 A. Or at the time of the last patient out.

25 Q. Well, it actually says "before." Right?

—Fruehauf - Cross—

1 A. Yes.

2 Q. Okay. So before the last patient was out of the clinic,  
3 the way you interpret this paragraph, one or more of the  
4 declarants would have had to have done some analysis to see  
5 some indication of success of the trial, correct?

6 A. I think that was really saying that they could have.

7 Q. They could have?

8 A. And that could have led to them reaching the conclusion  
9 of a successful test.

10 Q. You say they could have because you don't know, correct?

11 A. No, I don't know.

12 Q. So you're speculating.

13 A. Yes.

14 Q. Now, you don't know who actually prepared this English  
15 language document, I take it?

16 A. I would imagine an attorney.

17 Q. Okay. A U.S. Attorney?

18 A. I don't know.

19 Q. All right. Now, do you -- are you familiar with the  
20 extent to which the three declarants speak English?

21 A. No.

22 Q. All right. Do you know whether a translation was  
23 prepared for them?

24 A. I don't know.

25 Q. Now, in speculating as to how one might see an indication

—Fruehauf - Cross—

1 of success from 99-03 prior to October 2, 2001, you went  
2 through some analysis of comparing blinded data to historical  
3 efficacy data. Do you recall that?

4 A. Yes, sir.

5 Q. Okay. I want to try and understand that in a moment but  
6 before I get there, you have no basis to believe that any of  
7 the declarants actually did that analysis, correct? Well, I'm  
8 sorry, let me rephrase that.

9 You have not seen any documents or evidence otherwise  
10 indicating that, in fact, the declarants had done that  
11 analysis, correct?

12 A. This is the only document that I can look at that  
13 suggests that they had successfully tested it, and to make  
14 that statement, I was trying to come up with, well, how could  
15 you have done that, if the data are blinded, and that's what I  
16 did.

17 Q. So the answer to my question is yes?

18 A. This is the only -- this document is what I was going by.

19 Q. Okay. And you've not seen any --

20 A. Other document.

21 Q. -- Helsinn documents or other evidence indicating that  
22 Helsinn or the declarants ever did the analysis you posited?

23 A. No, sir.

24 Q. No, sir, you haven't seen that?

25 A. No, sir, I haven't seen them.

—Fruehauf - Cross—

1 Q. Okay. I just wanted to understand the "no."

2 A. Yes, sir.

3 Q. Okay. Let's take a look at your Fruehauf Demonstrative  
4 Slide 9.

5 Now, you have a 70 percent in the bar, the red bar for  
6 historical efficacy of ondansetron; is that correct?

7 A. Yes, sir.

8 Q. And you have that drawn lower than the bar that shows  
9 74.4 percent blinded data average for the other three,  
10 correct?

11 A. Well, for ondansetron and the other two.

12 Q. Yeah.

13 Now, and you believe it's fair to represent that the 70  
14 percent as being lower than the 74.4 percent?

15 A. Yes. By 4.4 percent.

16 Q. Okay. Now, you -- I believe you explained that you  
17 obtained that 70 percent historical number from DTX-0288-0064.  
18 Do you recall that?

19 A. Correct.

20 Q. Okay. But you didn't, as I recall, actually refer to --  
21 bring up the exhibit to show us how you obtained that number.  
22 Do you recall that?

23 A. Yes, sir.

24 Q. So I want to try and understand that number. If we could  
25 pull up DTX-0288-0064. And let's go down to the lower

—Fruehauf - Cross—

1 paragraph, the number of patients.

2 THE COURT: So this is from the 99-03 Phase III study  
3 report? Yes?

4 MR. O'MALLEY: Can you answer the Judge's question?

5 THE WITNESS: Yes. 99-03.

6 MR. O'MALLEY: 99-03. Okay.

7 BY MR. O'MALLEY:

8 Q. And I'll represent this was the only place I could find  
9 that 70 percent, namely, and the sentence says, "The sample  
10 size was based on the assumption of a responder rate of 70  
11 percent in the palonosetron and ondansetron groups and a  
12 difference of no more than 15 percent in the complete response  
13 rate." Is this the basis for your 70 percent historical  
14 evidence?

15 A. Well, the basis is actually from a prior part, but this  
16 is where the number came out because they did the calculations  
17 based on the meta-analysis. The meta-analysis is on the prior  
18 page.

19 We looked at 7,000 patients, and I briefly did explain  
20 that, but -- so the 70 percent is the number they use for the  
21 clinical trial to design the power of the study. They  
22 needed --

23 Q. Now --

24 A. This is a non-inferiority study.

25 Q. Now, the 70 percent isn't referred to as a historical

—Fruehauf - Cross—

1 efficacy from ondansetron. There is no designation of that  
2 number as historical. Do you see that?

3 A. Well, you'd have to go back, as I said, to the prior  
4 page, at the bottom, where they describe the methods they used  
5 to get the 70 percent number.

6 Q. My question is far easier. At least in this section,  
7 it's not described as a historical efficacy number, correct?

8 A. Because they've already explained how they got it.

9 Q. Uh-huh.

10 Now, did you find this number or was it pointed out to  
11 you by contrast by counsel?

12 A. I take personal responsibility for finding this myself.

13 Q. So you looked through the entirety of the document to  
14 glean a historical efficacy number for ondansetron?

15 A. Well, I wanted to understand the design of the study.  
16 And it's a non-inferiority study, so they have to have an  
17 assumption of what the comparator will do in the study, and  
18 then they have to be non-inferior to that assumption. You  
19 can't just do the study and say I'm going to put ten people on  
20 each arm and get an answer. You have to have how many people  
21 am I going to need in each arm and what will the response  
22 rates be of the control group, which is ondansetron. And so  
23 they're assuming that the control group, the ondansetron arm,  
24 will have a response rate of 70 percent based on the  
25 meta-analysis that's described on the prior page.



—Fruehauf - Cross—

1 THE COURT: When you say response rate of 70  
2 percent --

3 THE WITNESS: Control, control. So they say  
4 responder rate there, 70 percent in the sentence. But what  
5 responder rate really means is they respond to the drug by  
6 having complete control of their -- complete control of the  
7 emesis. Complete response is how they refer to it, complete  
8 response, so you didn't feel nauseated and you didn't need a  
9 rescue medication.

10 BY MR. O'MALLEY:

11 Q. Now, let's turn to DTX-0288.0100. And let's look at  
12 Table 7.1.1.2. And you understand this is from the same  
13 document?

14 A. Well, that is from the same document, yes.

15 Q. And the heading says, comparison of complete response,  
16 zero to 24 hours, between the ondansetron group and modelled  
17 historical ondansetron group. Do you see that?

18 A. Yes.

19 Q. And with respect to the data for modelled historical  
20 ondansetron, do you see there is a complete response rate  
21 stated there of 79.3 percent?

22 A. Yes.

23 Q. Now --

24 THE COURT: And then the next column is the  
25 ondansetron dosage and the number of people and the result in

—Fruehauf - Cross—

1 this Phase III, 99-03 study.

2 THE WITNESS: Yes, ma'am.

3 THE COURT: Correct? 68.6.

4 THE WITNESS: 68.6.

5 BY MR. O'MALLEY:

6 Q. Now, if we can pull up PTX-075. PTX, the demonstrative.

7 Now, with this demonstrative, we inserted into your  
8 form of demonstrative --

9 A. Um-hum.

10 Q. -- the number that was listed for the historical  
11 ondansetron complete response rate, do you see that, of 79.3  
12 percent?

13 A. Yes.

14 Q. And you see that was -- that was about 5 percent greater  
15 than the actual response rate for the combined blinded data?

16 A. Yes.

17 Q. Do you see that?

18 A. Yes.

19 Q. Now, again, you have no basis for believing anyone at  
20 Helsinn did this particular analysis that you've described?

21 A. No. I only -- what we saw that they had stipulated or  
22 stated in their patent -- claim --

23 THE COURT: Declaration.

24 THE WITNESS: Thank you, declaration -- that they had  
25 successfully tested the hypothesis.

—Fruehauf - Cross—

1 BY MR. O'MALLEY:

2 Q. Now, you began your opinions today that a POSA in the  
3 field of clinical science would have known that palonosetron  
4 at .25 mgs reduces CINV, correct?

5 A. Yes.

6 Q. Now, you did not describe to the Court all of the  
7 documents that that POSA would have available to it to judge  
8 the efficacy of palonosetron in humans, correct?

9 A. I'm not sure what all the documents would be.

10 Q. Well, let's turn to DTX-0276. And you recognize this  
11 document, correct?

12 A. Yes, I do.

13 Q. And the parties have referred to this throughout the  
14 litigation as *Tang 1998*; is that correct?

15 A. Yes, sir.

16 Q. Now, as of the critical date, you understand that *Tang*  
17 *1998* contains the only publicly available, fully peer-reviewed  
18 human clinical data regarding the efficacy of palonosetron?

19 A. Yes.

20 Q. I'm sorry. Do you understand that?

21 A. I understand that this was the only prior art that was  
22 published for I.V. palonosetron and that it was for an  
23 indication of postoperative nausea and vomiting, after  
24 hysterectomy.

25 Q. But my question was a little broader.

—Fruehauf - Cross—

1           As of the critical date, it's actually the only  
2 peer-reviewed, publicly available publication containing human  
3 efficacy data regarding palonosetron, period, correct?

4   A.   Human efficacy data for postoperative nausea and  
5 vomiting.

6   Q.   Of any type.

7   A.   But that's what was studied here.

8   Q.   Of any type.

9           THE COURT:   You mean any type of emesis?

10           MR. O'MALLEY:   Correct.   Can you answer that  
11 question?

12           THE WITNESS:   It could be.   It probably is.

13 BY MR. O'MALLEY:

14   Q.   Okay.   Now, we discussed the fact at your deposition that  
15 experts in this case have taken the position that any dose  
16 that's effective for CINV for a drug of this class is  
17 generally going to be higher than the dose required for PONV,  
18 and you weren't able to really take issue with that.   Do you  
19 recall that?

20   A.   No, I did -- I didn't agree with it.

21   Q.   You didn't -- fair enough.   You didn't have any basis to  
22 agree or disagree, correct?

23   A.   No, I did.   I said that I didn't necessarily agree with  
24 it and that there are different doses for different drugs, and  
25 you know, for example, ondansetron is used at 16 milligrams

—Fruehauf - Cross—

1 for postoperative nausea and vomiting, and 8 milligrams, half  
2 the dose, for chemotherapy-induced nausea and vomiting.

3 But in my deposition, I said that, you know, there are  
4 different doses and different drugs and I didn't -- I wouldn't  
5 take that as a hard-and-fast rule.

6 Q. Well, I just want to make sure I understand. You have no  
7 basis to dispute the general proposition that the approved  
8 dosages for treating CINV are generally higher than the  
9 approved dosages for PONV for the 5-HT<sub>3</sub>s, correct?

10 THE COURT: Are you just --

11 THE WITNESS: Are you asking me that question now?

12 THE COURT: Pardon me, sir.

13 THE WITNESS: I'm sorry.

14 THE COURT: You just gave an example?

15 MR. O'MALLEY: I'm just asking -- I need to know  
16 whether he -- I didn't understand his example.

17 BY MR. O'MALLEY:

18 Q. Do you have any basis to dispute that?

19 A. Yes.

20 Q. All right. Can we pull up the transcript, please, 138:23  
21 and 139:7.

22 "QUESTION: But my question was simple. Just the  
23 approved dosages. Are you aware that for this class of drugs,  
24 generally, CINV has higher approved dosages than PONV?

25 "MR. WONG: Objection.

—Fruehauf - Cross—

1 "THE WITNESS: That may be.

2 "QUESTION: You have no basis to dispute that?

3 "ANSWER: I have no basis to dispute it or confirm it."

4 Did I read that correctly?

5 A. Yes.

6 Q. Now, the authors of Tang concluded that with respect to  
7 the PONV they studied, only the 30-microgram-per-kilogram dose  
8 was effective in reducing postoperative nausea and vomiting.

9 Are you aware of that?

10 A. I wouldn't agree with that characterization.

11 Q. Are you aware that they concluded that, whether or not  
12 you agree with it?

13 A. No, they concluded that it was the dose that  
14 significantly decreased the incidence of vomiting.

15 Q. Now, let's go to the abstract. And on the right,  
16 beginning towards the bottom, implications. "Implications:  
17 RS-25259, a long-acting 5-HT<sub>3</sub> antagonist, was effective in  
18 reducing postoperative vomiting only at the largest dose  
19 studied, 30 micrograms per kilogram. However, RS-25259 had no  
20 antinausea activity, and the larger doses were associated with  
21 an increased incidence of headaches in the postoperative  
22 period." Do you see that, sir?

23 A. Yes.

24 Q. And there is no word "significantly." Do you see that?

25 A. In that sentence, there is not.

—Fruehauf - Cross—

1 Q. Now, let's go to the -- let's go to DTX-0276-0005. And  
2 midway down the page, there is -- at the margin there is a  
3 sentence beginning "Only the largest dose." "Only the largest  
4 dose of RS-25259, 30-microgram-per-kilogram I.V. was effective  
5 in decreasing vomiting and the need for rescue antiemetic  
6 drugs during the first 24 hours after major gynecologic  
7 surgical procedures." Correct?

8 A. Yes.

9 Q. And no use of the word "significantly," correct?

10 A. Correct.

11 Q. And right above that, the sentence says that "These  
12 results," referring to the summary results, "suggest that  
13 smaller doses of RS-25259 are ineffective in preventing PONV."  
14 Do you see that?

15 A. Yes.

16 Q. Now, in turning to the conclusion, right above the  
17 references, "In conclusion, RS-25259,  
18 30-microgram-per-kilogram was effective in preventing PONV in  
19 women undergoing major gynecologic surgery. However, it did  
20 not decrease postoperative nausea or improve patient  
21 satisfaction." Do you see that?

22 A. Yes.

23 THE COURT: Just a second, counsel.

24 PONV, postoperative nausea and vomiting, in one  
25 breath they say it's effective in preventing that; then they

—Fruehauf - Cross—

1 say yeah, but not the nausea part.

2 MR. O'MALLEY: Yeah.

3 THE COURT: Right, Doctor?

4 THE WITNESS: Yes, ma'am.

5 BY MR. O'MALLEY:

6 Q. Right. And recall, complete response is vomit -- I  
7 shouldn't be testifying -- but vomiting or retching; isn't  
8 that true, Doctor?

9 A. Yes, sir.

10 Q. Okay. And then that secondary indication, you've  
11 testified that they often use a questionnaire, how do you  
12 feel?

13 A. Yes. I think they would rather have worded it preventing  
14 POV, rather than PONV, and then it wouldn't be confusing. I  
15 think that's a misstatement.

16 Q. Yeah.

17 Now, nowhere in --

18 THE COURT: Just a second. In the Phase III trial,  
19 99-03, when you get a complete response figure, as I  
20 understood the testimony earlier today, Doctor, complete  
21 response includes the questionnaire of the patient, are you  
22 experiencing nausea, and they have to say no in order to  
23 qualify as complete response.

24 THE WITNESS: Correct.

25 THE COURT: In that Phase III trial.



—Fruehauf - Cross—

1 THE WITNESS: Yes.

2 THE COURT: Okay. Thank you.

3 MR. O'MALLEY: Okay. Thank you.

4 BY MR. O'MALLEY:

5 Q. Now, in -- nowhere else in Tang do they use the word

6 "effective" in connection with any other dosage, correct?

7 Other than 30 microgram per kilogram?

8 A. Okay. I'll say yes.

9 Q. Okay. Now, again, to catch us up, 30 microgram per  
10 kilogram was the dosage that in Study 2330 was the only dose  
11 showing a statistically significant complete response versus  
12 the combined control group. Do you recall that?

13 A. Yes.

14 Q. And, again, that 30 microgram per kilogram corresponds to  
15 2 milligrams, correct?

16 A. I believe that's correct.

17 Q. And then we saw subsequently in the meeting minutes of  
18 1998 involving Helsinn and Syntex people that with respect to  
19 the recommendation to go forward in Phase III, at that point  
20 in time there was still a recommendation to still use that  
21 2-milligram dose. Do you recall that?

22 A. Yes.

23 Q. Now --

24 THE COURT: But that would be for the CINV, not for  
25 the PONV?

—Fruehauf - Cross—

1 MR. O'MALLEY: Yes.

2 THE WITNESS: Yes, ma'am.

3 MR. O'MALLEY: Yes. Correct, Your Honor.

4 BY MR. O'MALLEY:

5 Q. Now, let's turn to DTX-0264. And let's turn to the  
6 0264.0009, the table of data.

7 Now, again, you provided testimony about that table,  
8 correct?

9 A. Yes, sir.

10 Q. And the table is called preliminary data; is that right?

11 A. It just says, "Table, Summary of Complete Response."

12 Q. Within the document it's referred to as preliminary data;  
13 do you recall that?

14 A. It may be, yes.

15 Q. And there were no statistics in connection with this  
16 particular preliminary data; is that right?

17 A. Not in this table.

18 Q. And there is no safety data presented for these  
19 preliminary results; is that correct?

20 A. Not in this table.

21 Q. And, again, this is just the preliminary results from  
22 99-03; is that correct?

23 A. These are the results for what is stated here, which is  
24 the complete response proportion in the intent-to-treat  
25 cohort.

—Fruehauf - Cross—

1 Q. From Study 99-03, correct?

2 A. Yes.

3 Q. And, as you testified previously, in order to get a MEC  
4 indication, there would also have to be satisfactory results  
5 from 99-04, correct?

6 A. Well, I mean, I'm not testifying with respect to FDA  
7 approval. I'm testifying with respect to the reduction in the  
8 risk of nausea and vomiting.

9 Q. When my question involves indication, my question is --  
10 implicitly involves FDA approval. Do you understand --

11 A. Oh, okay, yes.

12 Q. -- to get FDA approval for an indication of MEC, they  
13 needed satisfactory results from 99-04?

14 A. Yes, sir.

15 Q. Okay. Now, you heard Dr. Calderari testify yesterday  
16 that these results just made them hopeful. Did you hear him  
17 testify to that?

18 A. Was that yesterday?

19 Q. Oh, gosh, I don't know, honestly, if it was yesterday or  
20 the day before. But did you hear that testimony?

21 A. I remember him saying that he was an organic chemist and  
22 he wasn't a clinician.

23 Q. But you heard him say it just made Helsinn hopeful?

24 A. That these results made them hopeful?

25 Q. Just made them hopeful, yeah. Do you recall that?

—Fruehauf - Cross—

1 A. No.

2 THE COURT: Seeing these preliminary results made  
3 them hopeful?

4 MR. O'MALLEY: Made them hopeful.

5 THE WITNESS: Okay, they were hopeful.

6 BY MR. O'MALLEY:

7 Q. But you believe it would demonstrate to a POSA in the  
8 clinical science that, in fact, palonosetron would have been  
9 known to -- at .25 mgs would have been known by that POSA to  
10 reduce CINV, correct?

11 A. Well, I guess it's possible that since he speaks  
12 Swiss-Italian and he's translating into English, we don't know  
13 would what the word really means in his mind but it could be  
14 that he thinks that he's won, that this is going to be  
15 approved based on these results, and that going forward  
16 everything is going to be great.

17 Q. So it's -- in your mind, when he said hopeful, he got the  
18 English mixed up; he actually meant "we won" and that's what  
19 you believe?

20 A. I don't know. I don't know what's in his mind and I  
21 would say that it's difficult to interpret simply because of  
22 the language difficulties.

23 Q. I see.

24 You previously testified about a press release from  
25 2000. Do you recall that?

—Fruehauf - Cross—

1 A. Yes, sir.

2 Q. And do you know that the quote that you cited to was  
3 attributed to a Luigi Baroni, Senior Director of Scientific  
4 Affairs; do you recall that?

5 A. Yes, sir.

6 Q. And do you know anything about his English language  
7 capability?

8 A. No, I do not, sir.

9 Q. Could we pull up DTX-0040? And let's make that a little  
10 bit larger, if we can. And let's scroll up to the date.

11 And do you see this is January 16, 2002?

12 A. Yes, sir.

13 Q. Do you see that date?

14 A. Um-hum.

15 Q. Do you see the title is "Helsinn and MGI Pharma announce  
16 completion of pivotal Phase III trials of palonosetron"? Do  
17 you see that?

18 A. Yes.

19 Q. And do you see that this is about a week or so later than  
20 the date of the August Consulting letter that attached that  
21 table of preliminary results? Do you see that?

22 A. Yes. Yes.

23 Q. Now, if you go down to the third paragraph, it states,  
24 "We are pleased to have completed all patient treatment and to  
25 have begun analysis of the data collected in the palonosetron

—Fruehauf - Cross—

1 3 clinical program," said Luigi Baroni, Senior Director of  
2 Scientific Affairs Division at Helsinn. Do you see that?

3 A. Yes.

4 Q. And that's pretty accurate in light of the August  
5 Consulting letter we saw, correct, as of this moment in time?

6 A. That they had done the analysis by the date that is on  
7 this press release.

8 Q. Well, strictly speaking, it says, "We have begun the  
9 analysis." Do you see that?

10 A. Yeah, I mean --

11 Q. Do you see that?

12 A. Yes.

13 Q. Okay.

14 A. They had seen the SAS output. They began the analysis of  
15 the data collected.

16 Q. Begun.

17 A. Yes.

18 Q. That's what it says.

19 A. Yes.

20 Q. Not finished. Okay.

21 And then it goes on to say, "The Phase II clinical  
22 trial results were promising." Do you see that?

23 A. Yes.

24 Q. "And we are hopeful that the Phase III palonosetron data  
25 will demonstrate that it can make a difference for cancer

—Fruehauf - Redirect—

1 patients suffering from CINV." Correct?

2 A. Yes.

3 Q. And this press release was publicly available, just like  
4 the 2000 press release, correct?

5 A. Yes.

6 Q. I have no further questions.

7 THE COURT: I would just like to know what this word  
8 "pivotal" --

9 THE WITNESS: Yes, ma'am.

10 THE COURT: -- that you've been exchanging back and  
11 forth means to you, sir.

12 THE WITNESS: To me, the pharma company -- well, in  
13 the drug development process, the pivotal trial is the trial  
14 that is what the FDA is looking for to give the NDA license.

15 THE COURT: Okay.

16 REDIRECT EXAMINATION BY MR. WONG:

17 Q. Dr. Fruehauf, Mr. O'Malley began by asking you about your  
18 educational training and background in pharmacology.

19 A. Yes, sir.

20 Q. Do you recall that?

21 A. Yes, sir.

22 Q. When did you get your pharmacology degree?

23 A. My Ph.D. was in 1996 in pharmacology.

24 Q. And when did you start that degree?

25 A. I started that degree in an M.D./Ph.D. program in 1980 --

—Fruehauf - Redirect—

1 I started the laboratory part in 1984.

2 Q. So how many years in total did you spend studying  
3 pharmacology?

4 A. A long time. So from 1984 to 1996.

5 THE COURT: You got your M.D. what year, sir?

6 THE WITNESS: 1985.

7 THE COURT: So you just kept going on this, working  
8 on this Ph.D. --

9 THE WITNESS: (Nods head.)

10 THE COURT: -- for another decade really.

11 THE WITNESS: My advisor wanted additional  
12 experiments, and so I carried out more experiments as a  
13 fellow, and then I carried out experiments after I came to UC  
14 Irvine, and eventually, he was satisfied.

15 THE COURT: And you prevailed.

16 THE WITNESS: And I prevailed.

17 BY MR. WONG:

18 Q. During the course of your career, how many clinical  
19 trials have you been involved with?

20 MR. O'MALLEY: Asked and answered, Your Honor.

21 THE WITNESS: Yes.

22 MR. O'MALLEY: In the direct.

23 MR. WONG: I think the original question was how many  
24 clinical trials were you currently involved with.

25 THE WITNESS: Yes.



—Fruehauf - Redirect—

1 MR. WONG: This one is over the course of your  
2 career.

3 THE WITNESS: Yes.

4 BY MR. WONG:

5 Q. How many clinical trials have you been involved with?

6 A. Hundreds.

7 Q. And your clinical practice at UC Irvine, how long have  
8 you had that clinical practice?

9 A. 1993.

10 Q. So how long -- how many years?

11 THE COURT: What year?

12 THE WITNESS: 1993. So I've been taking care of  
13 patients and seeing patients on trials for five years as a  
14 fellow at the NCI, and then from 1993 to the present time is  
15 22 years. So 27 years I've been working with patients on  
16 clinical trials.

17 BY MR. WONG:

18 Q. Okay. And have you been principal investigator on any of  
19 those trials?

20 A. Yes, I have.

21 Q. How many -- do you recall how many -- how many times  
22 you've been a principal investigator on a clinical trial?

23 A. Well, so, at an institution, the person who's running the  
24 study at the institution is the principal investigator, and  
25 there are other principal investigators at other places. And

—Fruehauf - Redirect—

1 so whoever is running that at an institution is the PI, and so  
2 I've been PI on, you know, 50 or 60 trials.

3 MR. WONG: Let's go back to DTX-0 264. Let's go to  
4 Page 9, the Appendix I, the preliminary analysis. Blow up the  
5 data, please, on Page 9.

6 BY MR. WONG:

7 Q. Dr. Fruehauf, do you recall Mr. O'Malley asking you about  
8 the data here?

9 A. Yes, sir, I do.

10 Q. Let's start with ondansetron, okay? Is ondansetron  
11 effective for reducing CINV in patients?

12 A. Yes, it is.

13 Q. And in this data, how many people got ondansetron?

14 A. 185.

15 Q. And ondansetron is effective for this indication; is that  
16 correct?

17 A. It's approved for --

18 Q. This indication?

19 A. It is approved for chemotherapy-induced nausea and  
20 vomiting, and it is approved for postoperative nausea and  
21 vomiting.

22 Q. Okay. So -- and in the zero- to 24-hour row, what  
23 percentage of people getting ondansetron had that primary  
24 output?

25 MR. O'MALLEY: I'll just object, it is beyond the

—Fruehauf - Redirect—

1 direct. I asked no questions about this table about  
2 ondansetron.

3 THE COURT: I'll permit it.

4 THE WITNESS: 69 percent. I'm rounding up.

5 BY MR. WONG:

6 Q. Now let's go back to palonosetron, 0.25 milligrams. What  
7 was the response rate for this dosage form, .25 milligrams?

8 A. The complete response rate was 81 percent.

9 Q. And how did that compare to the ondansetron response --  
10 response rate?

11 A. It's 13 percent better or -- 12 percent better.

12 Q. And how does that inform your opinions on -- on whether  
13 or not the 0.25 milligrams was effective to reduce CINV?

14 A. I would say that it was not inferior, which is what the  
15 study was designed to show; therefore, if it's not inferior,  
16 it's at least equivalent; and here, these numbers show it may  
17 be a little better.

18 Q. And for the numbers for palonosetron, 0.25 milligrams,  
19 how many patients received that dose?

20 A. 189.

21 Q. And so 81 of those 189 patients --

22 THE COURT: 81 percent.

23 BY MR. WONG:

24 Q. 81 percent of those 189 patients had a complete response;  
25 is that correct?

—Fruehauf - Redirect—

1 A. Yeah, 153 out of the 189 had complete response.

2 Q. So, based on this data, did 153 people have a reduction  
3 in the likelihood of CINV?

4 A. They certainly did.

5 Q. Okay. Let's go to DTX-0276, the Tang article. Let me  
6 start with this. Is Tang a study on palonosetron for PONV?

7 A. No, it is not.

8 Q. I'm sorry. For CINV?

9 A. I mean, it is not a study for CINV. It is a study for  
10 postoperative nausea and vomiting.

11 Q. And do you have any opinions as to the difference between  
12 a study on PONV and a study on CINV?

13 A. Yes. And I think that I, during my deposition, I  
14 explained why it's so different, because you have -- in a  
15 postoperative setting, you have the anesthesia, which is the  
16 major cause of the nausea and vomiting, and as the anesthesia  
17 is leaving the brain, and then you have the pain medications  
18 that the patient is given because of the surgery. And, of  
19 course, we know that morphine and morphine-type drugs cause  
20 nausea and vomiting.

21 So we have a bunch of things going on in those  
22 patients, and it's complicated, and there are a lot of  
23 variables in terms of the people that go in the study, what  
24 their predisposition is to the anesthesia to cause nausea and  
25 vomiting. There's a lot of variables.

—Fruehauf - Redirect—

1 Q. And for a CINV study, are there as many variables as  
2 there are in a PONV study?

3 A. It's a little easier. They're not getting pain  
4 medication, so you don't have to treat the nausea from the  
5 pain medicine. You're really focused on the nausea from the  
6 chemotherapy.

7 THE COURT: And no anesthesia either, right?

8 THE WITNESS: And no anesthesia.

9 BY MR. WONG:

10 Q. So let's look at the actual data in the Tang study.  
11 Let's go to 276, Page 4, Table 2.

12 MR. WONG: Can you blow up -- can you highlight the  
13 data for the 3-microgram-per-kilogram dose?

14 BY MR. WONG:

15 Q. And this is the .25 milligram dose; is that correct?

16 A. Yes.

17 Q. What does this data report?

18 A. It shows of the 40 people, the percent that vomited  
19 within zero to 24 hours was 30 percent, so that would --

20 THE COURT: The percent that -- that did vomit.

21 THE WITNESS: Yes.

22 THE COURT: So this is not a control --

23 THE WITNESS: So the flip side would be 70 percent  
24 control and -- at 24 hours versus 30, 26 percent vomited, so  
25 there's a 4 percent difference between the percent that

—Fruehauf - Redirect—

1 vomited.

2 BY MR. WONG:

3 Q. So in the Tang study, the patients that actually got the  
4 3 mg per kg dose, did they experience a reduction in PONV?

5 A. Well, if you look at the .1 which is similar to how they  
6 did the 2330 analysis in terms of the .1 was the low dose,  
7 we'll use that sort of as a control, so 44 percent vomited,  
8 versus 30 percent, so 14 percent reduction with the 3, and 26  
9 percent with the 30.

10 Q. Okay. And let's go to Page 3. Does the Tang reference  
11 actually talk about the lower doses and the effectiveness of  
12 lower doses? I can point your direction to the left column.

13 A. Okay. Now I can see it.

14 Q. About eight lines down, starting with the sentence  
15 "Although." Can you read that?

16 A. Although the need for rescue antiemetics within the first  
17 two hours was similar among all groups, 1, 3, 30, -- okay.  
18 So, although the need for rescue antiemetics within the first  
19 two hours was similar among all groups, 1, 3 and 30  
20 significantly decreased the antiemetic requirement compared  
21 with saline within the first 12 hours after surgery.

22 Q. And the 3-microgram-per-kilogram dose is a 0.25 milligram  
23 dose, correct?

24 A. Correct.

25 Q. Can we zoom out again, go to the right side, look at

—Fruehauf - Redirect—

1 right first paragraph. Can you read the sentence there?

2 A. Read which sentence?

3 Q. Sorry. The sentence starting RS-25259, 1.0 micrograms  
4 per kilogram.

5 A. All right. RS-25259, 1 milligram [sic] per kilogram I.V.  
6 was also effective in reducing the number of emetic episodes  
7 and the need for antiemetic rescue medication within 12 hours  
8 compared with saline.

9 Q. And is that a lower dose than the  
10 3.0-micrograms-per-kilogram dose?

11 A. That is a lower dose.

12 Q. So does Tang, the data and descriptions in Tang --

13 THE COURT: Counsel, I'm not sure you put your  
14 question right. I didn't understand it.

15 MR. WONG: The 1.0 microgram-per-kilogram dose is  
16 lower than the dose we're discussing, 3.0, and that's what  
17 this sentence is discussing.

18 Let me ask another question. Maybe that can --

19 THE COURT: I'm getting the 30 and the 3 in the  
20 text -- I can't follow it.

21 BY MR. WONG:

22 Q. Okay. Let's go back to Table 2 on the following page.  
23 So Tang, the conclusion in Tang only referenced the  
24 30-microgram-per-kilogram dose, is that correct, the one on  
25 the right?

—Fruehauf - Redirect—

1 A. Yes.

2 Q. And I'm going to ask about questions on the lower  
3 doses --

4 A. Yes.

5 Q. -- based on the data in Tang. And the lower doses  
6 include the 3-microgram-per-kilogram dose, correct?

7 A. Yes.

8 Q. And that's the 0.25 milligram dose that we're talking  
9 about?

10 A. Yes.

11 Q. Okay. So, based on the data in Tang, as well as the  
12 descriptions in Tang, do those data and descriptions tell you  
13 anything about the lower doses that were administered in Tang?

14 A. Yes. So we can see here, the 1 microgram per kilogram,  
15 which is one-third of the 3 which is the .25, we come down  
16 here, what they're saying is there was a significant decrease  
17 for the need for rescue anti-nausea medicines from the zero-  
18 to 12-hour point. It was identical pretty much across here  
19 for all three doses that the need for an extra pill was  
20 reduced by 40 percent. 70 percent of the people that got  
21 saline needed that extra pill, but only 43 percent of the  
22 people that got the palonosetron at those doses needed an  
23 extra rescue pill.

24 Q. So would a person of ordinary skill in the clinical  
25 sciences reading Tang, would they understand that doses less



—Fruehauf - Redirect—

1 than 30 micrograms per kilogram showed efficacy for this  
2 study?

3 A. Yes, they would.

4 Q. Okay. Let's go to the Syntex, let's start at the Syntex  
5 2330 study, and that is DTX-0227. And let's go back to the  
6 results on Page 15.

7 So Mr. O'Malley asked you about the  
8 30-microgram-per-kilogram dose, correct?

9 A. Yes.

10 Q. And he pointed out that only that dose had statistical  
11 significance, correct?

12 A. Yes.

13 MR. O'MALLEY: Objection, mischaracterized the  
14 question. But go ahead.

15 BY MR. WONG:

16 Q. He pointed out that that dose at percent complete control  
17 was statistically --

18 THE COURT: Can't hear you.

19 BY MR. WONG:

20 Q. He pointed out that that dose, 30 micrograms per  
21 kilogram, at the percent complete control, 24 hours, was  
22 statistically significant, correct?

23 A. Yes.

24 Q. And that number is 50 percent, correct?

25 A. Yes.

—Fruehauf - Redirect—

1 Q. The percentage for the three -- the .25 dose is 46  
2 percent, correct?

3 A. Correct.

4 Q. Does a difference in 46 and 50 percent affect your  
5 opinions as to whether or not the 3-microgram-per-kilogram  
6 dose reduces the likelihood of CINV in humans?

7 A. No.

8 Q. And why is that?

9 A. Because it isn't a statistical thing here. It's that we  
10 know that this is the plateau, and if you look across at these  
11 numbers, there's other points that are significant, and this  
12 is just one of them. But that was the primary endpoint, and I  
13 think that what -- the questions about statistical  
14 significance are really directed to FDA and using this as a  
15 pivotal study, and I'm really opining on, did -- was it known  
16 that the drug reduced nausea and vomiting at that dose, and it  
17 was.

18 THE COURT: The 3 dose.

19 THE WITNESS: At the 3. This is a reduction,  
20 compared to, you know, only 24 percent had control and, you  
21 know, we've talked about, you know, what saline would do.  
22 Nobody is going to be controlled.

23 So I think a person of ordinary skill would look at  
24 that 46 and say that that is the lowest effective dose, and I  
25 think my testimony substantiates over and over again that in

—Fruehauf - Redirect—

1 various documents, they concluded that -- Helsinn concluded  
2 that .25 was the minimal effective dose, and FDA agreed with  
3 them and allowed them to go forward in Phase III with that  
4 minimally effective dose.

5 BY MR. WONG:

6 Q. Okay. And so, just to be sure we're clear, the Syntex,  
7 Syntex scientists who performed this study concluded that 3  
8 micrograms per kilogram was among the effective doses based on  
9 this data; is that correct?

10 A. Yes, sir.

11 Q. And you mentioned the FDA -- the meeting minutes with  
12 Helsinn. During those meeting minutes, Helsinn also based  
13 their decision to go with 3 micrograms per kilogram in the  
14 Phase III studies on the Syntex data; is that correct?

15 A. Absolutely.

16 Q. And Helsinn also went to then -- went to FDA and made a  
17 statement to say that this data clearly demonstrated that 3  
18 micrograms per kilogram was the minimum effective dose; is  
19 that correct?

20 MR. O'MALLEY: Objection, Your Honor. It's become  
21 counsel's testimony. These are all leading questions.

22 THE COURT: I'll let him answer this one and then  
23 we'll be done with leading questions.

24 THE WITNESS: Yes. The FDA, as I said just a minute  
25 ago, said, yes, take the .25 forward and .75 forward into the

—Fruehauf - Redirect—

1 three pivotal Phase III trials, and so they agreed that .25  
2 was an effective dose to be studied in Phase III.

3 BY MR. WONG:

4 Q. And did Helsinn also issue a press release in September,  
5 2000, stating that Phase II studies demonstrated efficacy in  
6 emesis?

7 A. Yes, they did.

8 Q. Let's go to PTX-2061. Before we get there, let me just  
9 take a step back.

10 Let's go to DTX-0015. These are the 1998 meeting  
11 minutes that we reviewed earlier; is that right?

12 A. Yes, sir.

13 Q. Okay. Let's go to the portion that Mr. O'Malley  
14 referenced to you, Page 9. I think it's right in the middle,  
15 CINE dosing.

16 A. Yes.

17 Q. And he took you to the first bullet point. Can you read  
18 that again?

19 A. "In a review of the study data, the  
20 3-microgram-per-kilogram dose may not be the most effective."

21 Q. Okay. Does that say that 3 micrograms per kilogram is  
22 not effective?

23 A. No. It just says it might not be the most effective.

24 Q. Is that consistent with the Syntex data that the  
25 3-micrograms-per-kilogram dose was among four that they found

—Fruehauf - Redirect—

1 to be effective?

2 A. Yes.

3 Q. Let's go to PTX-2016. And I think Mr. O'Malley directed  
4 your attention to -- okay.

5 Let's go to DTX number of the same document, DTX-1017.

6 And I think Mr. O'Malley asked you questions on Clinical  
7 Question Number 6 that's on Page 6 at the bottom.

8 THE COURT: This is the FDA and Helsinn meeting?

9 MR. WONG: Yes, the end of Phase II meeting.

10 BY MR. WONG:

11 Q. So Helsinn's questions are at the top; is that correct?

12 A. Yes.

13 Q. And is the FDA response below?

14 A. Yes.

15 Q. Okay. So can you read -- what is Helsinn asking in  
16 Clinical Question Number 6?

17 A. They want to know if the 2330 can be a pivotal study and  
18 use it to get approval. They want to know if it's sufficient  
19 to support the labeled claim.

20 Q. And when it says labeled claim, including high-dose  
21 cisplatin, is that for approval?

22 A. That's for approval.

23 Q. And what's the second question?

24 A. "Should a historical control analysis be conducted?"

25 Q. Okay. And --

—Fruehauf - Redirect—

1 THE COURT: What does that mean?

2 THE WITNESS: That's where we went back and we looked  
3 at, you know, how the 99-03, they came up with a historical  
4 control number for emesis control for ondansetron.

5 BY MR. WONG:

6 Q. And the Clinical Question 6, is Helsinn asking whether  
7 the 2330 study is sufficient to support whether palonosetron  
8 reduces the likelihood of CINV?

9 A. No.

10 Q. And the FDA's response, can you read the first bullet  
11 point, starting, "due to the lack"?

12 A. "Due to the lack of a dose response in this study, these  
13 data are inadequate to serve as a pivotal efficacy support,  
14 although they may be useful as supportive data."

15 Q. So what does it mean where FDA is saying for 2330 data is  
16 not -- is inadequate to serve as pivotal efficacy support?

17 A. That they won't get approval just for that one study.

18 THE COURT: In other words, Phase II is not enough?

19 THE WITNESS: In this case, this Phase II study was  
20 not enough.

21 THE COURT: Could I just ask, since we're there  
22 again, I didn't understand this phrase, "due to the lack of a  
23 dose response in this study." What does that mean to you,  
24 Doctor?

25 THE WITNESS: So, I think it did have the dose

—Fruehauf - Redirect—

1 response. I think it was just a misunderstanding on the part  
2 of the reviewer because --

3 THE COURT: You mean Phase II had a dose response?

4 THE WITNESS: Yes, because we saw that the low doses  
5 had a low effect. And then the next set of doses were all  
6 equivalent. And you just have to --

7 THE COURT: So there was --

8 THE WITNESS: So there was an increased effect with a  
9 higher dose which is a dose response.

10 THE COURT: All right. But, still, the FDA was not  
11 satisfied with the Phase II.

12 THE WITNESS: I think that was really -- they weren't  
13 going to be -- you know, we don't usually in America, in our  
14 FDA, approve studies just on one Phase II study. We usually  
15 ask for a little more. But I think that it's interesting that  
16 they did allow them, for regulatory purposes, to use it in  
17 support of their one Phase III study for highly emetogenic  
18 chemotherapy. So it was ultimately --

19 THE COURT: Whoa, whoa. In support of their one  
20 Phase III study for highly emetogenic -- they still had to do  
21 a Phase III study for highly emetogenic, didn't they?

22 THE WITNESS: One. So they only had to do one for  
23 highly emetogenic because they were able to use this one as a  
24 second study in support of that indication.

25 THE COURT: Was the Phase II directed to the highly

—Fruehauf - Redirect—

1   emetogenic?

2               THE WITNESS:   Yes, ma'am.   So this study was done on  
3   the highly emetogenic, and it was used in combination with  
4   99-05 for two studies to support the label, whereas 99-03 and  
5   99-04 were two studies for the moderately emetogenic  
6   chemotherapy.

7   BY MR. WONG:

8   Q.   So, just to be clear, is Helsinn asking in this Question  
9   6 whether or not the study, the Phase II study, 2330 alone was  
10   sufficient to get approval for a labeled claim including  
11   high-dose cisplatin?

12   A.   Yes.   So it says, "Is 2330 sufficient to support the  
13   labeled claim including high-dose cisplatin?"   That was their  
14   question.

15   Q.   They wanted to skip Phase III.

16               MR. O'MALLEY:   Leading.

17               MR. WONG:   I'll rephrase.

18               THE WITNESS:   And I think that means they wanted to  
19   get approval just on their --

20               THE COURT:   Sustained.   You don't have to answer.

21               THE WITNESS:   Okay, sorry.

22   BY MR. WONG:

23   Q.   Just one last point.

24               So, at the last bullet point we stopped at, to serve as  
25   pivotal efficacy support, but what is stated in the



—Fruehauf - Redirect—

1 parentheses?

2 A. That's what I was saying, that although they may be  
3 useful as supportive data -- so the data were good and were  
4 ultimately used. Those data were used for approval of the  
5 drug for the highly emetogenic indication in combination with  
6 the Phase III study.

7 Q. Okay. Let's go to --

8 MR. WONG: Can you put up PTX-297? An Exhibit  
9 Mr. O'Malley showed.

10 BY MR. WONG:

11 Q. Do you remember this abstract that Mr. O'Malley showed  
12 you?

13 A. Yes, I do.

14 Q. Okay. And let's just confirm the date. What is the  
15 publication date of this abstract?

16 A. Probably June 23rd, 2002.

17 Q. Okay.

18 MR. WONG: Let's go to the second page, Page 2. And  
19 you can blow up the top.

20 BY MR. WONG:

21 Q. Just to confirm, was this for PALO -- was this the study  
22 results for PALO-99-04?

23 A. Yes.

24 Q. And does the abstract contain only the study data for  
25 PALO-99-04?

—Fruehauf - Redirect—

1 A. Yes.

2 Q. Does the abstract contain any other data from any of the  
3 other two clinical trials?

4 A. No.

5 Q. So, just based on this data alone, for one Phase III  
6 trial, would that satisfy your understanding of what Dr. Saab  
7 is requiring?

8 A. No.

9 Q. Okay. Why is that?

10 A. Because he said you need two confirmatory Phase III  
11 trials.

12 Q. And --

13 THE COURT: Well, they had the other one. This paper  
14 doesn't say --

15 THE WITNESS: No.

16 THE COURT: -- doesn't pull out those results, right,  
17 of 99-03?

18 THE WITNESS: Correct.

19 BY MR. WONG:

20 Q. To the best of your understanding, was any other Phase  
21 III trial published in the art between 2002 and 2003?

22 A. No.

23 Q. Do you recall what the date of completion of the final  
24 study report was for PALO-99-04?

25 A. August, 2002, I believe.

—Fruehauf - Redirect—

1 Q. And if we go to the analysis, the section above. So this  
2 data was an analysis that was performed prior to the final  
3 study report being completed?

4 A. Yes.

5 Q. Okay. And --

6 THE COURT: Which data? Your question refers to --

7 MR. WONG: The data in this table that is published  
8 on --

9 THE COURT: In that abstract?

10 MR. WONG: In this abstract.

11 THE COURT: In the meeting abstract?

12 MR. WONG: Yes.

13 BY MR. WONG:

14 Q. The abstract June, 2002. This data was published -- was  
15 this data published before the final study report for  
16 PALO-99-04 was written?

17 A. I believe it was.

18 Q. So this was preliminary with respect to the final study  
19 report?

20 A. Yes.

21 Q. Okay. And, based on this data, what were Helsinn  
22 scientists able to report in the conclusion?

23 MR. WONG: If you can blow up the conclusion.

24 THE WITNESS: They were able to conclude that  
25 palonosetron was effective at reducing the risk of emesis.

—Fruehauf - Recross—

1 BY MR. WONG:

2 Q. And this was before the final study report was written?

3 A. Correct.

4 THE COURT: So this would be a chart of preliminary  
5 data?

6 THE WITNESS: Well, as I said before --

7 THE COURT: No, no.

8 THE WITNESS: The data are final. When the data is  
9 locked, that's it. And so this data was an analysis that was  
10 done on the locked data for 99-04 and presented at a meeting,  
11 but they hadn't written their final report yet. So there were  
12 other things, statistics and other things that might be done  
13 to analyze it.

14 MR. WONG: Thank you. No further questions.

15 RECROSS EXAMINATION BY MR. O'MALLEY:

16 Q. Pull up DTX-0264 again. Now, let's go to the table, I  
17 think the third page or so. Was it 009? There we go.

18 Now, you were talking about the ondansetron data. Do  
19 you recall that?

20 A. Yes.

21 Q. Now, this is data that was generated through 99-03,  
22 correct?

23 A. Yes.

24 Q. This isn't a historical efficacy data for ondansetron,  
25 correct?

—Fruehauf - Recross—

1 A. Correct.

2 Q. Now, you said that the data showed non-inferiority of  
3 palonosetron, correct?

4 A. Yes.

5 Q. Now, then you showed -- then you stated that it maybe  
6 even shows that palonosetron's a little better. Do you recall  
7 that?

8 A. Yes.

9 Q. Now, you're aware that a non-inferiority study cannot be  
10 used to show superiority, correct?

11 A. Correct.

12 Q. Now, let's talk about Tang. Tang, and correct me if I  
13 heard you wrong, but I believe I heard that you don't believe  
14 that cancer patients in CINV -- experiencing CINV would also  
15 be on pain medications?

16 A. You know, most of my patients who are getting  
17 chemotherapy are not taking high doses of I.V. pain  
18 medications at the time they're getting their chemotherapy.

19 Q. At the moment they're getting their chemotherapy?

20 A. Correct.

21 Q. But they're getting pain medications, these cancer  
22 patients, at other times, correct?

23 A. Some of them.

24 Q. Yeah.

25 THE COURT: Including emetic-type pain meds?

—Fruehauf - Recross—

1 BY MR. O'MALLEY:

2 Q. Opioids?

3 A. Yeah. So what happens is, when you're on a chronic  
4 opioid, you have what's called tachyphylaxis which is you get  
5 used to the side effects. So the nausea event from a morphine  
6 goes down over time, and so the people that are chronically  
7 treated for pain do not have the nausea from the pain  
8 medicine. It's the acute phase of giving it. So if  
9 postoperatively, they're given the morphine, they have that  
10 acute reaction.

11 Q. Now, going back to the MASCC abstract, I think it was  
12 PTX-0297. Now, counsel for Teva made the point that this is  
13 preliminary data. Did you hear that?

14 A. He did say that.

15 Q. Now, as I believe you've discussed today, you don't  
16 expect the data to change from the preliminary data to the  
17 final data; in fact, I think you've stated so strongly as it  
18 can't, correct?

19 A. Well, you have your data, and it is the data. Then you  
20 have your analysis of the data. And you could do different  
21 types of analysis.

22 Q. So --

23 A. So the preplanned analysis is the critical analysis  
24 that's in the protocol that is required for the FDA.

25 Q. So with respect --

—Fruehauf - Recross—

1 A. And you can do it -- the first time you do it, I wouldn't  
2 call it preliminary. I would call it the first analysis of  
3 the locked database.

4 Q. So with respect to the preliminary data in here, it might  
5 have changed from here to the final study report?

6 A. I think the point was that --

7 Q. Yes or no? Could it have changed?

8 A. No.

9 Q. No. Thank you.

10 THE COURT: You mentioned that there's something  
11 about statistics, that they can do some more statistical  
12 analysis --

13 THE WITNESS: Yes.

14 THE COURT: -- after they get the preliminary data?

15 THE WITNESS: Yes.

16 THE COURT: But it doesn't change the raw numbers?

17 THE WITNESS: No.

18 THE COURT: Anything else?

19 MR. WONG: No further questions.

20 THE COURT: Thank you.

21 THE WITNESS: Thank you very much.

22 THE COURT: Thank you for traveling, Doctor, and safe  
23 travels home.

24 THE WITNESS: Thank you, ma'am.

25 (The witness left the stand.)

—Fruehauf - Recross—

1 MR. LOMBARDI: And Your Honor -- yes.

2 THE COURT: I'll see counsel at the side off the  
3 record.

4 (A sidebar discussion was held off the record.)

5 (Proceedings adjourned at 3:58 p.m.)

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